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Hazard Evaluation for New Bedford Harbor

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EXECUTIVE SUMMARY

It is well established for many PCB-induced toxicities in animals that the toxic potency of a PCB mixture increases with the average chlorine content of the mixture. Mounting scientific evidence now indicates that carcinogenic potential in animals is another toxicity for which potency varies with the average chlorine content of the commercial PCB mixture. In spite of this information, the U.S. Environmental Protection Agency (USEPA) continues to regulate all PCB mixtures according to the toxicity of those which contain 60% chlorine. This is in contrast to the accurate approach that USEPA has already adopted for dealing with polychlorinated dibenzodioxins (PCDDs), where USEPA recognizes congener differences in toxicity and assigns differences in toxic potency (called Toxic Equivalency Factors or TEFs) to various PCDD congeners. This dichotomy in approach to PCDD congeners and PCB mixtures exists even though PCB mixtures have undergone more extensive toxicity testing than have the separate PCDD congeners.

We have reviewed both the human epidemiologic evidence and the animal evidence of the potential for carcinogenicity which currently exists for the commercial PCB mixtures of 42%, 54% and 60% chlorine content. This review confirmed that there exist distinct differences in the animal carcinogenic potential of these mixtures, and that these differences are of sufficient magnitude to warrant separate classifications of PCB mixtures, both qualitatively and quantitatively, according to their average chlorine content. On the basis of these differences and the evidence provided by epidemiological studies, we have qualitatively classified the carcinogenic potential of these three PCB mixtures according to the guidelines currently used by the IARC (International Agency for Research on Cancer) and the USEPA.

Several studies have examined the causes of mortality among persons occupationally exposed to PCBs. The data resulting from these mortality studies performed to date have not provided evidence of carcinogenicity in humans from exposure to PCBs. Most of the studies are negative on this point. In each of the studies where positive associations between PCBs and carcinogenicity were

suggested, weaknesses in the studies did not permit a causal association to be either proved or dismissed. In both the Bertazzi and Brown studies, the authors acknowledge serious shortcomings in their data, such as the fact that correlations between dose or reasonable latency period and cancer incidence were absent in both studies. In addition, potential confounders were not controlled for or excluded in any of the studies reported to date. Until larger epidemiological studies can be completed, that is, until a larger number of deaths in the cohorts studied become available, the collective PCB epidemiology data must be considered to provide inadequate evidence of carcinogenicity. Therefore, for both the IARC and USEPA classification schemes, the animal evidence of carcinogenicity for each PCB mixture becomes the deciding factor in the final classification of the PCB mixture being considered.

It is quite clear from the available animal cancer literature concerning 42% chlorine PCB mixtures that they do not exert a carcinogenic response when chronically administered to rats or mice. While Schaeffer et al. (1984) did note an increased incidence of neoplastic nodules, the biological relevance of this finding is severely limited by the fact that these neoplasms had not progressed to benign or malignant tumors after a lifetime of exposure (i.e., the reported lesions appear to have had no carcinogenic potential). Because there is but a single negative lifetime study, at a single dose and in a single species, the data for animal carcinogenicity of 42% chlorine mixtures should be judged as providing either inadequate or no evidence of carcinogenicity according to both the IARC and USEPA classification schemes. This would result in an IARC classification of 42% PCBs as either Group 3 (inadequate evidence of carcinogenicity) or Group 4 (evidence suggesting a lack of carcinogenicity) chemicals. Since 42% PCBs are not genotoxic, and have yielded negative results in three studies testing two species, the Group 4 classification is warranted. Similarly, these classifications of the animal and human data should result in a USEPA categorization of 42% PCB mixtures as Group D chemicals (not classifiable as to human carcinogenicity). Again, the lack of genotoxic potential and three negative studies in two species strengthen this conclusion.

The animal carcinogenicity studies of 54% chlorine PCB mixtures are more difficult to interpret. The results of a lifetime bioassay of Aroclor 1254 conducted for the National Cancer Institute (NCI) were reported in 1978 and indicated that there was not a carcinogenic potential for the rat strain tested. Confirmatory evidence for the lack of carcinogenicity of 54% chlorine PCB mixtures was provided by the results of Ito and coworkers in their 1974 publication of an 8 month study. While an increased incidence in mouse liver tumors has been reported in two different studies, several features of this response limit its relevance. These features are: 1) the tumorigenic response was limited to male mice; 2) the tumorigenic response was not seen at slightly lower doses causing less severe liver effects; and 3) even though the rat studies employed either a limited number of animals or a less than lifetime exposure duration, one of these studies tested much higher doses for a longer period of time than the mouse studies and still the rat data were negative. In our review of the mouse data we have also noted the general scientific concern for positive mouse liver tumor data, especially when: 1) the data is sex and dose specific, 2) it occurs at doses inducing a condition of chronic tissue injury, and 3) it is not supported by positive findings in other species. After considering all of this evidence, we conclude from the animal data that there is limited evidence of carcinogenicity for PCB mixtures of 54% chlorine content. Under the IARC classification scheme this category is reserved for chemicals which induce *lesions of uncertain neoplastic potential* or neoplasms *which may occur spontaneously in high incidences in certain strains*. Given this and the inadequate human evidence, it is concluded that 54% chlorine PCBs should be classified as Group 3 chemicals under the IARC classification system. The supporting evidence to consider as the basis for altering this classification, i.e., lack of genotoxic potential and conditions of chronic toxicity in the target organ, tends to strengthen the Group 3 classification.

It is concluded that the data for animal carcinogenicity from exposure to 54% chlorine mixtures should also be classified as no better than limited evidence under the USEPA classification system. This classification results from conflicting interpretations of the one lifetime rat bioassay and from the fact that the mouse studies suffer from *inadequate duration of exposure, inadequate period of follow-up, too few animals, and inadequate reporting,* all experimental design

features which relegate a study to one of limited evidence in the USEPA classification system. This along with the inadequate evidence from human data, the lack of genotoxic potential and conditions of chronic toxicity in the target organ, leads to a classification of 54% chlorine PCB mixtures as Group C chemicals using the USEPA scheme.

Concerning the animal carcinogenicity of 60% PCB mixtures, hepatocellular carcinoma has been reported in three separate studies providing sufficient evidence of carcinogenicity (Kimbrough et al., 1975; Schaeffer et al., 1984; Norback and Weltman, 1985). There are, however, a number of consistent features of these data that make the data of limited biological relevance to humans. To summarize, these features are: 1) the tumors occur very late in the life of the animal at apparently maximally tolerated doses (MTD); 2) 60% chlorine PCBs never increased the total tumor load, and while increasing the incidence of liver tumors also decreased the incidence of other neoplasms (other studies also suggest antitumor activity with specific tumors); 3) the tumors did not behave like malignant tumors, i.e., no metastases were reported even though an approximate 50-90% hepatocellular carcinoma incidence was reported in two studies; and 4) the tumors were not life-shortening; on the contrary PCB-treated animals tended to live significantly longer than the untreated animals. Given the limited biological relevance of these tumors, the lack of genotoxic potential, and the fact that chronic systemic and liver toxicity occurs at the doses tested, it is concluded that the classification of 60% PCB mixtures should be no higher than 2B under the IARC system and B2 under the USEPA system.

The qualitative assessment of the PCB toxicologic data described above has been used to quantitatively assess the hazards posed by exposure to PCBs. Because 60% chlorine PCBs have demonstrated carcinogenic potential in animals, the quantitative assessment used the conservative, no-threshold approach endorsed by the USEPA in spite of the fact that animal responses were of limited biological relevance and PCBs are not genotoxic. Regarding the perceived carcinogenic potency 60% chlorine PCB mixtures, however, recent information has led us to a different value than that calculated by the USEPA. The USEPA has chosen to quantify the carcinogenic potential for all PCB

compounds as though these compounds were a single entity. The derived cancer potency factor (q_1^*) of 7.7 $(mg/kg/day)^{-1}$ is based upon data from only one of the three 60% chlorine PCB bioassay data sets available (the study by Norback and Weltman). It includes neoplastic nodules as a part of the carcinogenic response to the PCB mixture and uses surface area as the scaling factor for extrapolating from animals to man. Unfortunately, there are certain methodological flaws in the experimental design of the Norback and Weltman study which should preclude its use to derive a cancer potency estimate for PCBs. Foremost among these flaws is the use of partial hepatectomy, a liver tumor promoting stimulus, in a considerable number of animals. However, rather than completely dismiss the Norback and Weltman study, we have combined the cancer potency factors derived from all three studies as a means of mitigating the potential problems associated with any one of the studies. We have also incorporated recent recommendations for improving the risk assessment approach currently used by the USEPA. This reanalysis of the bioassay data for 60% chlorine PCB mixtures results in a q_1^* of 0.18 $(mg/kg/day)^{-1}$ and as mentioned is based on the geometric mean of the individual cancer potency factors which were derived from the benign and malignant tumor incidence reported in the three published studies.

Since the qualitative assessment of the data for 42% chlorine PCB mixtures led to the conclusion that these mixtures are not carcinogenic in animals, other toxic endpoints were sought from which an estimate of the safe daily exposure could be derived. Similarly, the qualitative assessment of 54% PCBs suggested only limited carcinogenic potential in animals, allowing some latitude in the manner in which safe exposure estimates should be derived for these mixtures. With this in mind, we have completed an evaluation of toxicity data for commercial PCB mixtures of 42% and 54% chlorine content which examined non-oncogenic toxicities. These mixtures were evaluated with regard to:

- Hepatotoxicity
- Dermatotoxicity
- Immunotoxicity
- Thyroid toxicity
- Reproductive and developmental toxicity.

Other sensitive tissues, species and data from studies of other commercial mixtures were also considered. Sensitive species identified included mink, mouse, rat, rabbit and monkey. Generally on exposure to PCBs, six organ systems or processes were affected; the liver, skin, thyroid, immune system, reproductive system and development. For both 42% and 54% chlorine PCB mixtures, mink, rat and monkey were identified as the most sensitive species. The information on 42% chlorine PCB mixtures indicated that hepatotoxicity in the rat, reproductive and systemic toxicity in the mink and dermatotoxicity in the monkey were the most sensitive endpoints and resulted in NOAELs very similar in magnitude (100, 112 and 90 μg/kg/day, respectively). The geometric mean of these three endpoints, 100 μg/kg/day, was assumed to represent the NOAEL for the systemic toxicities of 42% chlorine PCBs. For 54% chlorine PCB mixtures, the sensitive species were determined to be the same and with the exception of the monkey, the sensitive toxicologic endpoints were the same. The geometric mean of these values, 48 μg/kg/day, was assumed to represent the NOAEL for non-oncogenic toxicities of 54% chlorine PCB mixtures.

Clinical studies of occupationally exposed persons have failed to link the relatively high occupational exposures (where the highest and longest exposures of humans to PCBs have occurred) to any serious, chronic condition. Serum PCB concentrations in workers may be roughly 100 times those observed in the general population, and the study of these workers clearly represents the best opportunity for determining whether PCB exposure causes adverse health effects in humans. Several cohorts of occupationally-exposed workers have been examined for the presence or history of physical illness and have been subjected to a variety of clinical laboratory measurements. However, chronic exposure to PCBs in the occupational setting does not appear to produce any significant adverse human health effect, and the paucity of abnormal results in examined populations has been noted by several investigators. Thus, the occupational hazard associated with these compounds is still primarily one of skin problems, consisting usually of dermatitis or rashes and redness and an occasional case of chloracne.

In addition to the NOAELs derived from animal data human NOAELs were derived from the occupational studies. First, data from the occupational studies

reporting PCB air and surface concentrations were used to estimate daily exposures. From these data an estimated exposure of 3,600 µg/day was derived. Second, daily exposure estimates were also derived by taking a pharmacokinetic approach to reported occupational body burdens. Based on a half-life of one year, the daily occupational exposure was estimated to be 4,200 µg/day. Thus, remarkably similar estimates of daily exposure to PCBs in the workplace were generated from the available occupational data using two distinctly different approaches. As epidemiologic investigations have failed to demonstrate any chronic, irreversible adverse health effects in occupationally-exposed individuals receiving these doses, this exposure evaluation suggests the NOAEL in humans is at least 50-60 µg/kg/day.

Given that the estimate for the NOAEL in human exposure studies in the workplace, i.e., 50 µg/kg/day, approximates the NOAELs for 42% and 54% PCB mixtures in animal studies, it was unnecessary to derive an Allowable Daily Intake (ADI) or Reference Dose (RfD) for these mixtures from the animal data. Therefore, based on the NOAEL developed from occupational studies, and assuming that a safety factor of 10 is needed to protect sensitive individuals, an ADI of 5 µg/kg/day for 42% chlorine mixtures is derived. As the animal NOAELs suggested 54% chlorine PCB mixtures are more toxic than their lesser chlorinated counterparts, by a factor of 2-5, an additional 5-fold safety factor was used to derive an ADI of 1 µg/kg/day for 54% chlorine PCB mixtures. Other approaches for developing a human exposure limit for 54% PCB mixtures were considered, but as discussed in the last section of this report, these offered no obvious advantages over the approach taken here. In fact, these approaches typically generated a larger or less conservative ADI.

1.0 INTRODUCTION AND OBJECTIVES

In spite of the widespread distribution of polychlorinated biphenyls (PCBs) in air, water, soil, and foodstuffs and their subsequent deposition in the tissues of modern man, uncertainties remain regarding the toxicity of PCBs to humans. These uncertainties have spawned regulatory approaches to the cleanup of environmental PCB contamination which are largely based on data from animal studies. As such, PCB regulations suffer from the unavoidable problems associated with the extrapolation of results of animal studies to man. Regulation of PCBs is further complicated by the toxicological differences between commercial PCB mixtures, the composition of which varies widely. For example, 60% and 54% chlorine PCB mixtures are made up primarily of penta-, hexa-, and heptachlorinated biphenyl molecules. In contrast, 42% and lesser chlorinated PCB mixtures are composed primarily of tetra-, tri-, di-, and mono-chlorobiphenyl molecules. The United States Environmental Protection Agency (USEPA) has largely chosen to ignore the toxicological differences between different commercial mixtures of PCBs and regulate all PCB mixtures based primarily on the animal carcinogenicity of one commercial PCB mixture. Such a regulatory approach would be justified in the absence of data which clearly define the toxicological differences among commercial PCB mixtures. However, mounting scientific evidence indicates that differences do indeed exist in the carcinogenic potential and toxic potency of commercial PCB mixtures, suggesting that this regulatory approach is flawed. Specifically, there is good evidence for the carcinogenicity of 60% chlorine PCB mixtures in rats and hence there is a basis for regulating this mixture as a potential carcinogen. However, even with considerable animal testing, firm evidence for the carcinogenicity of other commercial PCB mixtures is lacking. As clear differences exist in either the potency of PCB mixtures or the toxic effects produced by PCB mixtures, a thorough toxicological evaluation of each commercial PCB mixture would lead to a more accurate portrayal of the potential human risks associated with exposure to the less toxic PCB mixtures. The intent of this document is to provide a separate evaluation for each individual PCB mixture, as defined by their average chlorine content, and to generate safe exposure guidelines that reflect the toxicological differences of these individual PCB mixtures.

Risk assessment is the process whereby a toxicological evaluation qualitatively and quantitatively describes the probability for adverse human health effects as a result of exposure to some chemical or group of chemicals. Risk assessment, therefore, is a basic tool used by regulators attempting to reach decisions governing the remediation of environmental contamination or the allowable level of a chemical contaminant in a particular environmental medium such as air or water.

The five basic steps of the risk assessment process are:

1. **HAZARD IDENTIFICATION** - The hazard identification summarizes the toxicological data base for the chemical of interest and identifies the potential adverse health effects observed in animal and human studies. An example of a hazard identification is the Toxicant Profile for PCBs (TERRA, 1988) prepared prior to this hazard evaluation.

2. **HAZARD EVALUATION** - The hazard evaluation is an analysis of the dose-response relationships, potency, species variation and toxicological mechanisms of a chemical. Specifically, the following points are to be analyzed:

    - An evaluation of the types of toxic responses and sensitive organs and tissues.
    - Investigation of species variation in toxic effects.
    - Examination of the mechanism(s) of toxicity.
    - A determination of the validity of the tests performed in animals and their relevance for extrapolation to man.
    - Comparison of animal test doses with the expected level of human exposure.
    - An evaluation of available data from long-term occupational exposures and human poisonings. Such an

evaluation may provide information regarding expected human effects and act as a test for extrapolations made from animal data.

3. **RISK ESTIMATION** - A risk estimation is often made as part of the hazard evaluation. A risk estimate is a quantitative assessment or modeling of the possibility (i.e., a determination of probability) that an adverse effect will occur at a specific dose of the chemical.

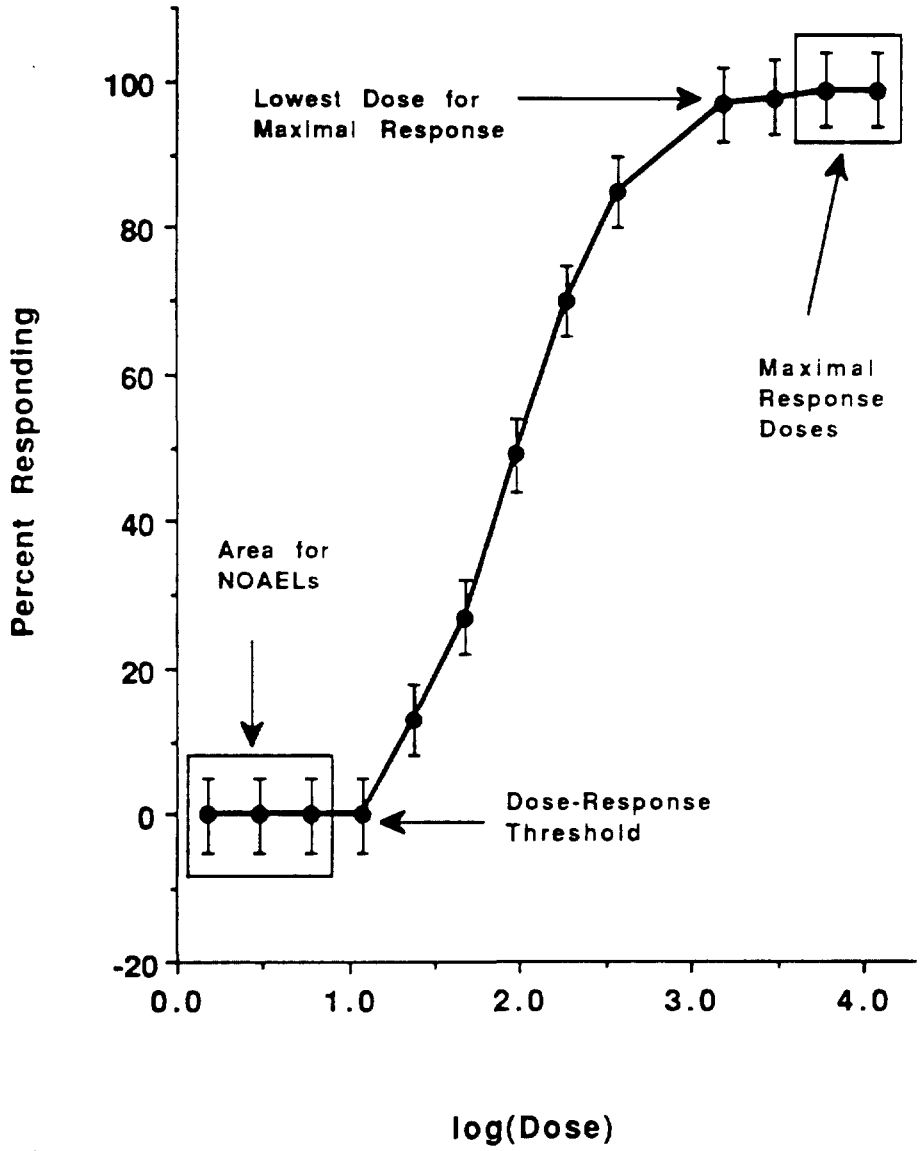
4. **EXPOSURE EVALUATION** - The exposure evaluation provides estimates of likely human exposure which may result from human contact with the affected environmental medium. The exposure evaluation takes into consideration site-specific characteristics which may affect the potential for human exposure to the chemical.

5. **RISK ASSESSMENT** - The risk assessment integrates the outputs of the exposure evaluation with the risk estimates for the chemical. This provides some determination as to the relative safety or hazard associated with the anticipated exposure.

Central to risk assessment is the demonstration of dose-response relationships. For the toxicologic endpoint being monitored (death, cancer, organ damage, neurobehavioral changes, *etc.*) a range of doses of the compound, providing a graded series of responses, must be utilized in the studies being reviewed (see Figure 1). In the linear portion of the dose-response curve, in this case doses of 10-1,000 [log(10) = 1 and log(1000) = 3], an increase in dose results in a proportional increase in response. Below or above the linear portion of the dose-response curve, the response is a constant regardless of the dose. At low doses a constant response (zero) is obtained because the dose is insufficient to elicit a measurable response. At high doses, saturation of receptors or the site of toxic action occurs limiting the response to the maximal response regardless of the magnitude of the dose administered. For purposes of establishing safe levels of exposure to a chemical, the most critical point on the dose-response curve is the **threshold dose**. The threshold dose is defined as the dose below which no effect occurs.

Figure 1

Hypothetical Dose Response Curve



The term, as used in this document, refers to that theoretical point between doses which produce an effect and those doses which do not. Current regulatory practice for nononcogenic effects is to analyze the toxicological data for the range of doses producing no adverse effect, identify or estimate the threshold dose, and apply safety or conversion factors to this dose to generate an acceptable daily intake (ADI) for humans. Uncertainty (safety) factors are typically used in the development of an ADI because the data being modeled (often animal data) provide less than ideal information concerning the actual dose-response relationship for the toxicity of concern in humans.

In practice, determination of the threshold dose is very difficult. Often, the only data available are for a few select doses spanning a considerable portion of the dose range. The threshold dose is usually assumed to be the highest NOAEL reported, although as a consequence of the doses selected for study, this may be substantially below the true threshold. In some cases, no NOAEL information is available. Under these circumstances, the NOAEL may be estimated as being some fraction of the lowest-observable-adverse-effect-level (LOAEL) for that chemical.

If some carcinogenic potential for the compound has been demonstrated, it is generally assumed that no threshold exists. That is, the carcinogenic response (cancer risk) is some function of dose such that zero risk is not achieved unless the dose is zero. Thus, the dose-response curve is considered to be some linear function of dose even at those doses too low to provide a measurable response. While this nonthreshold property of carcinogens may be a prudent assumption for some chemicals, it is an assumption that has never been proven. On the contrary, there are many carcinogens which experimentally demonstrate the potential for a threshold, and whose epigenetic mechanism suggests a true threshold must exist.

Finally a point which must be emphasized is that the process is **qualitative** as well as **quantitative**. The quantitative aspect of risk assessment is the generation of a numerical estimate of the safe level for chemical exposure. Often, this can be a range of values dependent on the assumptions used and the mathematical models employed. Qualitative risk assessment establishes the hazard of a

chemical exposure in relative terms. Certain findings in animal studies may be both dose- and species-dependent. The qualitative portion of the risk assessment evaluates the relative strength of the data and makes some determination as to the relevance of the finding to persons exposed at defined levels. For PCBs, a quantitative risk assessment will be performed including qualitative judgements concerning the applicability of animal studies to humans.

The objective of this hazard evaluation is to appraise all animal and human toxicological data associated with 54% and 42% chlorine commercial PCB mixtures. The adequacy of this information for deriving mixture-specific safe exposure guidelines for humans will be assessed, and safe doses for, or risk estimates of, the human health hazards possibly associated with PCBs will be derived.

2.0 TOXICITY OF 54% AND 42% CHLORINE PCB MIXTURES

The acute, subchronic, and chronic toxicity studies of separate PCB mixtures have been summarized in the Toxicant Profile for Polychlorinated Biphenyls (TERRA, 1988). The reader is directed to this Toxicant Profile for a more detailed discussion of the studies cited below.

2.1 A Review of the Nononcogenic Toxicities Observed in Animal Studies and the NOAELs/LOAELs Associated with These Toxicities

In the absence of good human data, the most prudent approach to derive an ADI is to base the calculation of NOAELs on a species thought to most closely mimic the human responses to the chemical. While clearly a reasonable approach, it is a self-defeating task; for without sufficient human data there is no basis for selecting the animal species which mimics the human condition. Additionally, species extrapolations are often made more difficult by the inevitable data gaps and inconsistencies among reported findings that may be uncovered during a thorough review of the toxicological literature. Therefore, in the process of selecting a study or studies as the basis for deriving an Allowable Daily Intake (ADI) for humans, qualitative decisions regarding the usefulness, applicability, and level of confidence the assessor places in the animal data being relied upon must also be made. Key factors such as study design, animal species tested, dose level, route of exposure, and study duration are critically examined. Ultimately, the choice of a study (or studies) as the basis for the calculation of an ADI must be the scientifically justifiable result of a thorough analysis of the available literature. The following review of animal toxicity studies of 54% and 42% chlorine PCB mixtures emphasizes the identification of sensitive target organs in each animal species and the doses producing either NOAELs or LOAELs in each target organ. In a subsequent section of the report, a qualitative analysis of these data will assess the final dose or estimated dose thought to reasonably approximate the probable human NOAEL for all of these toxicities. This dose, i.e., the best estimate of the NOAEL in humans based on animal studies, will then be used to derive an ADI for humans. This ADI may in turn be used to assess the relative safety or hazard of a given environmental exposure situation.

2.1.1 Target Organs and Sensitive Animal Species

Any attempt to identify the most sensitive target organ or organ system must be based on an evaluation of several studies, since no single study is adequate for this purpose. In general, the most sensitive target organ or organ system can be determined through a comparison of the lowest doses required to produce toxicity in various specific organs or tissues. For PCBs, the lowest dose required to produce a particular toxicity (also termed the lowest-observable-adverse-effect-level or LOAEL) can be ascertained from a number of existing studies. However, in using these studies to determine the most sensitive organ/tissue, two points must be recognized:

1) Organ toxicity comparisons should be made for specific commercial PCB mixtures, since commercial PCB mixtures are not equivalent in their toxicity. For example, the LOAEL for the hepatotoxicity of Aroclor 1254 could not be compared with the LOAEL for the immunotoxicity of Aroclor 1242 to find out whether the liver or immune system is more sensitive to PCB toxicity.

2) Information concerning toxicity in a specific organ/tissue for a specific PCB mixture is often available in more than one species. However, dose comparisons of organ sensitivity should be made within the same species as there are substantial differences among species in vulnerability to PCB toxicity.

A review of the animal toxicity data for PCBs reveals five major types of target organs for toxicity. These are: 1) the liver, 2) the skin, 3) the immune system, 4) the thyroid, and 5) the reproductive system. There are insufficient data to determine the most sensitive of these target organs or organ systems in each major test species for each commercial PCB mixture. For the purposes of establishing ADIs for 42% and 54% chlorine PCBs, the evaluation of animal toxicity information will focus primarily on the available data for these mixtures.

In the following sections, literature relevant to the determination of LOAELs for toxicity in these target organs will be briefly summarized and comparisons among species will be made, to the extent possible, from the available data. LOAELs are estimated based upon the lowest dose in a study, or among different studies, observed to produce a measurable effect. In some cases, this may be the

lowest dose tested, and the severity of the response observed at this dose may vary with the study. In order to facilitate species and target organ comparisons, an attempt has been made to express the exposure used in varying studies in terms of a common measure, dosage (in units of μg-PCB/kg body weight/day). In many cases, this involves some sort of conversion from the manner in which the dose is expressed in the original report. For example, in many studies exposure was from the addition of PCBs to the diet in specified concentrations such as 100 ppm. In order to estimate the daily dose resulting from ingestion, food consumption rates and average body weights for various species were assumed from Lu (1988). In some studies, PCB doses were administered at intervals less frequent than daily. For these studies, an "equivalent" daily dose was calculated by dividing the dose by the number of days in the dosing interval. While it is recognized that frequent, smaller daily doses may not in fact be toxicologically equivalent to less frequent, larger doses, concern for this potential difference is offset by the fact that PCBs are persistent, bioaccumulative compounds. As such, blood and tissue PCB levels are much less affected by these differences in exposure frequency than would be the case for chemicals which are rapidly cleared.

The subsequent descriptions of animal studies are organized by affected organ. These categories are hepatotoxicity (liver), dermatotoxicity (skin), immunotoxicity (immune system), thyroid toxicity, and reproductive and developmental toxicity. Under each category, organ toxicities are further subcategorized by PCB mixture. Information is summarized for each of the four laboratory animal species for which, in general, the most data are available, viz. mouse, rat, rabbit, and monkey. Information from other species has also been considered, and is discussed in section 2.1.7. Since many PCB mixtures from different manufacturers (e.g. Kanechlors, Clophens, Aroclors, etc.) have been utilized in these studies, the PCB Toxicant Profile (TERRA, 1988) may be referred to for specific information on the mixtures used.

2.1.2 Hepatotoxicity

Histopathologic evidence of liver injury associated with PCB administration has been observed in a variety of experimental animal species. In most cases, hepatotoxicity has been evaluated through direct histopathologic examination of the liver.

2.1.2.1 42% Chlorine PCBs

Mice: No evidence of hepatotoxicity was found in mice fed 42% chlorine PCBs at 3.75 or 37.5 ppm for six months (Aroclor 1242; Koller, 1977). Exposures to 100 ppm for 32 weeks (Kanechlor 300), 167 ppm for six weeks (Aroclor 1242), 250 ppm for 32 weeks (Kanechlor 300), 375 ppm for six months (Aroclor 1242), or 500 ppm for 32 weeks (Kanechlor 300) all were associated with signs of hepatic injury (Ito et al., 1973; Koller, 1977; Loose et al., 1978). The lowest dosage associated with hepatotoxicity in these studies was 100 ppm, which in mice is assumed to be equivalent to 15 mg/kg/day.

NOAEL: 5,625 µg/kg/day
LOAEL: 15,000 µg/kg/day

Rats: The lowest exposure to a 42% chlorine PCB mixture reported to produce hepatotoxicity is 5 ppm for six months (Bruckner et al., 1974a&b). Livers from these rats were enlarged an average of 20% and had small, lipid-containing vacuoles. Other studies using higher exposures to 42% chlorine PCB mixtures also noted hepatotoxicity (Miller, 1944; Ito et al., 1974; Burse et al., 1974; Allen et al., 1975; Jonsson et al., 1981). A dietary exposure to 5 ppm in rats is assumed to be equivalent to 0.5 mg/kg/day.

NOAEL: none reported
LOAEL: 500 µg/kg/day

Rabbits: Hepatotoxicity was found among rabbits administered Aroclor 1242, 300 mg once per week for 14 weeks (Koller and Zinkl, 1973). Higher doses administered as a single dose have also been found to produce evidence of hepatic injury (Miller, 1944). If 300 mg/week is converted to a daily dose, and a body weight of 2 kg is used, an estimated LOAEL of 21.4 mg/kg/day is calculated.

NOAEL: none reported
LOAEL: 21,400 µg/kg/day

Monkeys: There are no data with which to estimate a NOAEL or LOAEL.

2.1.2.2 54% Chlorine PCBs

Mice: Mice fed 3.75 ppm Aroclor 1254 for 6 months had normal liver histopathology, while mice fed 37.5 ppm had mild centrilobular granular degeneration and necrosis (Koller, 1977). Higher exposures -- 100 ppm Aroclor 1254 for 15 weeks; 100 ppm Kanechlor 500 for 32 weeks; 250 ppm Aroclor 1254 for 14 days or 15 weeks; 250 ppm Kanechlor 500 for 32 weeks; 375 ppm Aroclor 1254 for six months; 500 ppm Kanechlor 500 for 42 days or 32 weeks -- were consistently observed to produce evidence of hepatotoxicity (Ito et al., 1973; Sanders et al., 1974; Kimbrough and Linder, 1974; Koller, 1977; Tanimura et al., 1980; Talcott and Koller, 1983). The 37.5 ppm apparent LOAEL in mice is assumed to be equivalent to a dosage of 5.62 mg/kg/day, while the NOAEL is one-tenth of this dosage.

NOAEL: 562 µg/kg/day
LOAEL: 5,620 µg/kg/day

Rats: Rats fed 1 or 5 ppm Aroclor 1254 in a three generation study (62-274 days) occasionally had liver cell enlargement (Linder et al., 1974). Pigment, foamy cytoplasm, and fibrous strands were also observed in some livers from animals in these treatment groups. In another study, increased lipid droplets, marked proliferation of Golgi condensing vesicles containing lipoproteins, and decreased mitochondria were found in livers of rats fed 5 ppm Aroclor 1254 for five weeks (Kasza et al., 1978a). Hepatic enlargement was observed with 5 ppm dietary exposure for 5 weeks in one study (Garthoff et al., 1977), but another study found no hepatic enlargement with exposure to 1 or 10 ppm for 18 months (Keplinger et al., 1971). Other studies have also found evidence of hepatic abnormalities after higher exposures to 54% chlorine PCB mixtures. For example, exposure to 10 ppm in the diet has been reported to produce hepatic porphyrinic fluorescence (Zinkl, 1977); 20 ppm has been associated with hepatic enlargement (Carter, 1983), disseminated or focal necrosis (Baumann et al., 1983), enlarged hepatocytes with foamy cytoplasm and cytoplasmic inclusions (Kimbrough et al., 1974), and moderate fatty liver degeneration (Chu et al., 1977); 50 ppm has been observed to produce fatty liver degeneration and cytoplasmic vacuolization (Kasza et al.,

1978a); and 100 ppm has been reported to cause focal degeneration and hepatic necrosis (Allen et al., 1976), fatty liver (Grant and Phillips, 1974), and adenofibrosis and pigment accumulation (Kimbrough et al., 1972). The most consistent evidence indicates that the LOAEL for hepatotoxicity is 5 ppm dietary exposure. In one study, some hepatic changes were seen in a small percentage of mice treated with 1 ppm exposure, but the vast majority of mice at this dosage had no hepatic abnormalities. In another study, 1 ppm Aroclor 1254 was without effect on the liver. A 1 ppm dietary dosage appears to be near the threshold for hepatic effects, and probably approximates a maximum NOAEL. A dosage of 5 ppm in the diet is assumed to be equivalent to 500 μg/kg/day and 1 ppm equivalent to 100 μg/kg/day.

NOAEL: 100 μg/kg/day
LOAEL: 500 μg/kg/day

Rabbits: Probably the best study with which to identify a LOAEL is that of Street and Sharma (1975), who found hepatomegaly in rabbits fed 45.8 or 170 ppm Aroclor 1254 for 8 weeks, but no effect in rabbits fed 3.7 or 20 ppm. Consistent with this study, others have found evidence of hepatotoxicity with higher exposures, viz. 100 ppm for 5 days or 300 mg/kg administered once per week for 14 weeks (Koller and Zinkl, 1973; Wolff and Hesse, 1977). A 45.8 ppm dietary exposure in rabbits is assumed to be equivalent to 1.37 mg/kg/day.

NOAEL: 600 μg/kg/day
LOAEL: 1,370 μg/kg/day

Monkeys: Both cynomolgous and rhesus monkeys chronically exposed (cynomolgous: 12-13 months; rhesus: 27-28 months) to Aroclor 1254 at dietary levels equivalent to 200 μg/kg/day exhibited histopathologic evidence of hepatotoxicity (Tryphonas et al., 1986a&b). Cynomolgous monkeys also appeared to have hepatic injury when exposed to Aroclor 1254 in food equivalent to 5 mg/kg/day (Tryphonas et al., 1984).

NOAEL: none reported
LOAEL: 200 μg/kg/day

2.1.3 Dermatotoxicity

In a number of species, PCB exposure has been observed to produce dermal symptoms associated with hyperplasia and hyperkeratosis. In species such as the monkey, these effects may result in the appearance of acne-like pustules resembling the chloracne associated with high occupational exposure to PCBs in man.

2.1.3.1 42% Chlorine PCBs

Mice: There are no data with which to estimate a NOAEL or LOAEL.

Rats: No data are available from feeding studies. One study administered a 42% chlorine PCB mixture by subcutaneous and topical routes (Miller, 1944). Skin changes considered chloracne-like were noted after subcutaneous injection of 69 mg (single dose), and changes regarded as essentially those of low-grade irritation were seen after daily topical application of 34.5 mg of undiluted PCB mixture. It is difficult to express the dose associated with chloracne-like skin changes (69 mg subcutaneously as a single dose) in a form which lends itself to comparison with subchronic or chronic feeding exposures. However, it is important to note that these animals were also found to have significant abnormal liver and spleen histopathology. Therefore, for 42% chlorine PCB mixtures in these rats, the skin would not appear to be more sensitive than other target organs.

Rabbits: As with the rat, there are no data regarding dermal effects associated with feeding exposure to 42% chlorine PCB mixtures in the rabbit. Daily subcutaneous injection of 345, 690, or 1380 mg of a 42% chlorine PCB mixture for 10 days has been reported to produce changes described as chloracne-like (Miller, 1944). Topical application of undiluted PCBs (86 mg applied every other day for 7 doses followed by 172 mg applied every other day for 8 doses) caused a thinning of prickle cell layers and a thickening of cornified layers (Miller, 1944). It is difficult to extrapolate the localized dermal changes produced by application of extraordinarily high concentrations of PCB mixtures to possible dermal effects from other exposure situations such as ingestion. However, from the perspective of identifying sensitive organs or tissues, it is sufficient to note that the doses which caused these dermal effects were fatal to the rabbits in this study.

Monkeys: The limited data available make precise determination of LOAEL and NOAEL values impossible, although approximate ranges for these can be estimated. Two studies have fed rhesus monkeys Aroclor 1242 and reported dermatological findings, but the LOAEL is unclear from these studies. In one study, two rhesus monkeys exhibited thickening and reddening of the eyelids and rough and dull fur within two months of feeding with 400 μg/kg/day Aroclor 1242 (Becker et al., 1979). One monkey experienced similar symptoms at a lower dosage (120 μg/kg/day Aroclor 1242), although five rhesus monkeys in another study experienced no dermal symptoms when fed 200 μg/kg/day (McNulty et al., 1980). A representative LOAEL for 42% chlorine PCBs in monkeys would therefore appear to be between 120 and 400 μg/kg/day, and is probably closer to the upper end of this range. Rhesus monkeys fed Aroclor 1242 at 1 ppm in the diet (equivalent to approximately 40 μg/kg/day) for 133 days had no observable dermatological changes (McNulty et al., 1980). These animals continued to show no signs of dermal toxicity when the exposure was increased to 5 ppm (or about 200 μg/kg/day). The average dosage for their entire dosing regimen is estimated to be approximately 90 μg/kg/day, and a NOAEL for 42% chlorine PCB mixtures in monkeys can be anticipated to be at least in the 40 to 90 μg/kg/day range.

NOAEL: 40-90 μg/kg/day
LOAEL: 120-400 μg/kg/day

2.1.3.2 54% Chlorine PCBs

Mice: The LOAEL for dermal toxicity of 54% chlorine PCB mixtures is not readily determined from the available studies. Administration of approximately 40-50 or 320-400 mg/kg Aroclor 1254, four times per week for six weeks, produced no dermatologic changes (Puhvel et al., 1982). Converting this exposure to a daily equivalent (4/7), a NOAEL of roughly 180-230 mg/kg/day is calculated. However, the strains of mice used in this study (Skh:HR-1 and HRS/J) are uncommon and may be unusually resistant to PCB toxicity. Interestingly, 30-fold lower dosages of a French 54% chlorine PCB mixture (Phenoclor 54), approximately 5.7-7.1 mg/kg/day, were found to cause hyperkeratosis and hyperplasia in these mice. The much greater potency for dermal toxicity of this PCB mixture with PCB composition similar to Aroclor 1254 suggests that the French product may have

contained a dermatotoxic contaminant [Note: European PCB mixtures have been found to contain greater contamination with polychlorinated dibenzofurans than their American counterparts]. In another study, mice fed 200 ppm Aroclor 1254 for 20 weeks (or until papillomas developed) had hyperkeratinization, thicker pinnae, and erythema (Bell, 1983). A confounder in the latter study was the topical application of acetone, for which no provisions were made to determine its contribution to the dermal changes observed. A LOAEL based upon the Phenoclor 54 data is rejected because of evidence that the product may have been contaminated. A LOAEL based upon the study of Bell (1983) was selected as it is derived from a more conventional mouse strain than employed by Puhvel and coworkers, and it provides a more conservative estimate. A dietary exposure to 200 ppm in mice is assumed to be equivalent to 30 mg/kg/day.

NOAEL: Contradictory results prevent determination from current data.
LOAEL: 30,000 µg/kg/day

Rats: Erythema, crustiness, hyperkeratosis, perikeratosis on the ears, dorsum of nose and feet, and tail were observed in rats fed Aroclor 1254 at dietary levels of 10, 30 or 100 ppm for up to 20 weeks (Zinkl, 1977). The 10 ppm apparent LOAEL in this study is assumed to be equivalent to 1 mg/kg/day.

NOAEL: none reported
LOAEL: 1,000 µg/kg/day

Rabbits: There are no data with which to estimate a NOAEL or LOAEL.

Monkeys: Cynomolgous and rhesus monkeys were chronically fed Aroclor 1254 at 280 µg/kg five days per week, or about 200 µg/kg/day, for 12-13 months in cynomolgous monkeys and 27-28 months in rhesus monkeys (Tryphonas et al., 1986a&b). These monkeys had signs of dermal toxicity including loss or lifting of fingernails and enlargement of tarsal glands. More extensive exposures of cynomolgous monkeys to Aroclor 1254, in dietary dosages equivalent to 5 mg/kg/day, resulted in facial edema, lacrimation, and fingernail loss (Tryphonas et al., 1984). In another study, one monkey fed Aroclor 1254 at 100 µg/kg/day lost fingernails, although another fed the same dosage had no dermal effects (Truelove et al., 1982). A third monkey in this study, fed 400 µg/kg/day, also lost

fingernails. Consistent dermatotoxicity has been observed among monkeys fed 200 and 400 μg/kg/day, and half (one of two) of the monkeys fed 100 μg/kg/day exhibited signs of dermal toxicity. The LOAEL would therefore appear to be at or near 100 μg/kg/day.

NOAEL: none reported
LOAEL: 100 μg/kg/day.

2.1.4 Immunotoxicity

Possible immune system effects of PCBs have been evaluated in a number of ways. These include histopathologic examination of organs/tissues involved in the immune system (spleen, thymus, lymph nodes, etc.), effects on humoral or cellular immunity, and resistance to challenge from infectious agents.

2.1.4.1 42% Chlorine PCBs

Mice: Mice fed 5 or 100 ppm Aroclor 1242 for up to 18 weeks had decreased serum fibronectin concentrations, and splenic adherent cells derived from the mice fed 100 ppm showed diminished cell killing of mKSA tumor cells *in vitro* (Loose et al., 1981). However, no functional impairment of tumor cell killing *in vivo* occurred in mice fed either 5 or 100 ppm. Mice fed Aroclor 1242 at 167 ppm showed a diminished antibody response and were more sensitive to challenge with endotoxin (Loose et al., 1977; Loose et al., 1978a&b). A much higher, shorter exposure to Aroclor 1242 (1000 mg/kg single dose) has been shown to decrease splenic lymphocytes and cause splenomegaly (Carter and Clancey, 1980). The LOAEL and NOAEL derived from these studies are based upon the results on immune function *in vivo*.. Dietary exposure to 100 ppm (assumed to equal 10,000 μg/kg/day) had no effect on tumor cell killing, while diminished immune function was observed at 167 ppm (assumed to be equivalent to 25,000 μg/kg/day).

NOAEL: 10,000 μg/kg/day
LOAEL: 25,000 μg/kg/day.

Rats: There are no data with which to estimate a NOAEL or LOAEL.

Rabbits: Rabbits fed 300 mg Aroclor 1242 once per week for 14 weeks had diminished serum neutralizing antibody titers to pseudorabies virus (Koller and

Thigpen, 1973). This corresponds to a dosage of 150 mg/kg/week, or an average of 21.4 mg/kg/day.

NOAEL: none reported
LOAEL: 21,400 µg/kg/day

Monkeys: There are no data with which to estimate a NOAEL or LOAEL.

2.1.4.2 54% Chlorine PCBs

Mice: Mice exposed to 100, 200, or 400 ppm Kanechlor 500 in food for 3 weeks were found to be more susceptible to viral infections (Imanishi et al., 1980). In single dose experiments, mice administered 135, 250, or 500 mg/kg Aroclor 1254 had diminished plaque-forming cell response (Wierda et al., 1981; Lubet et al., 1986). Mice administered a single dose of 63 mg/kg Aroclor 1254 did not show this effect (Wierda et al., 1981). The lowest dosage observed to have effects on the immune system in these studies was 100 ppm in the diet, which in mice is assumed to be equivalent to 15 mg/kg/day.

NOAEL: none reported
LOAEL: 15,000 µg/kg/day

Rats: Rats fed Aroclor 1254 for 10 weeks at dietary levels of 50 or 500 ppm were observed to have altered interleukin-2 production and decreased NK cell cytotoxicity (Talcott et al., 1985; Exon et al., 1985). A dietary intake of 50 ppm in the rats in this study is assumed to be equivalent to 5 mg/kg/day.

NOAEL: none reported
LOAEL: 5,000 µg/kg/day

Rabbits: One study fed rabbits Aroclor 1254 at dietary dosages of 3.7, 20, 45.8, and 70 ppm for four weeks (Street and Sharma, 1975). Gamma globulins were not significantly depressed at any dosage, and none of the treatment groups had an altered skin reaction to tuberculin. Changes in numbers of globulin-producing cells were noted, but these were not clearly dose-dependent. Splenomegaly was observed with exposures of 45.8 ppm and 70 ppm. In another study, high, less

frequent administration of Aroclor 1254 (300 mg once per week for 14 weeks) was associated with diminished serum neutralizing antibody titers to pseudorabies virus (Koller and Thigpen, 1973). The estimated LOAEL is calculated from the 45.8 ppm exposure in the study of Street and Sharma (1975), and assumed in these rabbits to be equivalent to 1.37 mg/kg/day.

NOAEL: 600 µg/kg/day
LOAEL: 1,370 µg/kg/day

Monkeys: In one study, cynomolgous and rhesus monkeys were chronically fed Aroclor 1254 at exposures of 280 µg/kg five days per week, or equivalent to about 200 µg/kg/day. The duration of the study was 12-13 months for cynomolgous monkeys and 27-28 months for rhesus monkeys. Both types of monkey had lymphoreticular changes suggesting immune system effects (Tryphonas et al., 1986a&b). These changes in general consisted of atrophy or loss of lymphoid follicular centers. More extensive exposures of cynomolgous monkeys to Aroclor 1254, in dietary dosages equivalent to 5,000 µg/kg/day were accompanied by similar effects (Tryphonas et al., 1984). In another study, cynomolgous monkeys chronically exposed to 100 µg/kg/day had somewhat diminished antibody titer responses to injections of sheep red blood cells (Truelove et al., 1982).

NOAEL: none reported
LOAEL: 100 µg/kg/day

2.1.5 Thyroid Toxicity

Although the thyroid has not been widely examined as a potential target organ for toxicity, there has been some suggestion that it may be among the more sensitive organs to effects of PCBs. Effects on the thyroid have been evaluated both by direct histopathologic evaluation and by measurement of thyroid hormone (T3 and T4) kinetics. When considering the thyroid as a target tissue for PCBs, it must be recognized that thyroid effects can occur indirectly from hepatic effects as a consequence of increased clearance of thyroid hormones.

2.1.5.1 42% Chlorine PCBs

Mice: There are no data with which to estimate a NOAEL or LOAEL.

Rats: Rats fed 50 ppm Aroclor 1242 in the diet for 7 months did not have significant enlargement of the thyroid or changes in triiodothyronine kinetics (Sepkovic and Byrne, 1984). These rats were approximately 200 g at the beginning of the study. With food consumption based upon a mature rat (400 g body weight and 20 g/day food consumption), a NOAEL of 2,500 µg/kg/day is calculated, although this probably represents a slight underestimation of the actual dosage.

NOAEL: 2,500 µg/kg/day
LOAEL: none reported

Rabbits: There are no data with which to estimate a NOAEL or LOAEL.

Monkeys: There are no data with which to estimate a NOAEL or LOAEL.

2.1.5.2 54% Chlorine PCBs

Mice: There are no data with which to estimate a NOAEL or LOAEL.

Rats: Exposures as low as 5 ppm Aroclor 1254 in the diet for 8 weeks have been observed to be associated with thyroid changes (Collins and Capen, 1980a). These changes included enlargement of the thyroid, hypertrophy and hyperplasia of follicular cells, reduced follicular lumen, accumulation of large colloid droplets and irregular lysosomes, papillary and cytoplasmic projections, and diluted rough endoplasmic reticulum. Another study also found histological changes in the thyroid glands of rats treated with 5 ppm Aroclor 1254 for 5 weeks (Kasza et al., 1978b). Higher exposures have also been found to produce morphologic changes -- i.e. 50 or 500 ppm for 4 weeks (Collins and Capen, 1980a), 500 ppm for 42 days (Collins and Capen, 1980b), 50 or 500 ppm for 12 weeks (Collins et al., 1977), and 50 or 500 ppm for 5 weeks (Kasza et al., 1980b). Aroclor 1254 treatment has been reported to result in an increased rate of disappearance of thyroid hormone (Sepkovic and Byrne, 1984; Byrne et al., 1987), although this is a common effect of hepatic enzyme inducers and may be due to increased elimination (Bastomsky, 1974). These studies indicate a LOAEL equivalent to dietary exposure

to 5 ppm. A 5 ppm dietary intake in rats is assumed to be equivalent to 500 µg/kg/day.

NOAEL: none reported
LOAEL: 500 µg/kg/day

Rabbits: There are no data with which to estimate a NOAEL or LOAEL.

Monkeys: No enlargement of the thyroid was observed in four cynomolgous monkeys fed Aroclor 1254 at dosages equivalent to 200 µg/kg/day (Tryphonas et al., 1986b). One-half (2/4) of rhesus monkeys fed Aroclor 1254 equivalent to 200 µg/kg/day for 27-28 months had enlarged thyroids (Tryphonas et al., 1986a), and all of the rhesus monkeys fed dietary levels of Aroclor 1254 equivalent to 5,000 µg/kg/day whose thyroids were examined (5/6) had enlarged thyroids with hyperplasia (Tryphonas et al., 1984).

NOAEL: none reported
LOAEL: 200 µg/kg/day

2.1.6 Reproductive and Developmental Toxicity

The potential reproductive and developmental effects of PCBs have been extensively studied, though much less for 42% chlorine PCBs than for 54% chlorine PCBs. LOAELs may vary for a given mixture and species depending upon the endpoint examined, i.e. parameters relating to male or female reproduction, or to growth and development. For the purposes of this analysis, reproductive and developmental LOAELs have been individually determined where data permit.

2.1.6.1 42% Chlorine PCBs

Mice: There are no data with which to estimate reproductive or developmental NOAELs or LOAELs.

Rats: Reproductive- There are no studies indicating doses producing adverse effects of 42% chlorine PCBs in rats. Offspring from dams administered 30 mg/kg/day of Aroclor 1242 on days 14-20 of gestation showed no adverse effects on male or female reproduction (Gellert and Wilson, 1979). No effect on uterine

weight was observed in rats administered from 1 to 1000 mg/kg Aroclor 1242 as a single dose (Gellert, 1978). The highest doses examined in each of these studies represent NOAELs for 42% chlorine PCBs ranging from 30,000 to 1,000,000 µg/kg/day.

NOAEL: 30,000 - 1,000,000 µg/kg/day
LOAEL: none reported

Developmental- Female neonates administered 100 mg/kg Aroclor 1242 1-2 days after birth subsequently had no abnormalities with respect to age at vaginal opening, or the fraction of animals anovulatory or with persistent estrus (Gellert, 1978). This represents a NOAEL of 100,000 µg/kg/day.

NOAEL: 100,000 µg/kg/day
LOAEL: none reported

Rabbits: Reproductive- In one study, Aroclor 1242 administered at a dosage of 300 mg/week for 14 weeks had no effect on uterine weight (Koller and Zinkl, 1973). A daily equivalent dose, based upon a body weight of 2 kg as reported in the study, would be about 21,000 µg/kg/day. This dosage represents a NOAEL for reproductive effects in rabbits.

NOAEL: 21,000 µg/kg/day
LOAEL: none reported

Developmental- No studies are available.

Monkeys: There are no data with which to estimate reproductive or developmental NOAELs or LOAELs.

2.1.6.2 54% Chlorine PCBs

Mice: Reproductive- In one study, mice fed 100 ppm Aroclor 1254 for 108 days had a decreased conception rate (Welsch, 1985). Lesser exposures to Aroclor 1254 (10 ppm) have been observed to have no effects on conception rate (Welsch, 1985), litter size, birth interval, or number of litters per female (Linzey, 1987). With respect to possible male reproductive effects, a 200 ppm dietary exposure for 15 days had no

effect on testes weights, preputial glands, or vesicular glands (Sanders et al., 1977). A LOAEL of 100 ppm in mice is assumed to be equivalent to 15 mg/kg/day 54% chlorine PCBs; a NOAEL of 10 ppm would be one-tenth this dosage.

NOAEL: 1,500 µg/kg/day
LOAEL: 15,000 µg/kg/day

Developmental- No effects on the rate of malformation, number of resorbed fetuses, number alive at birth, or on fetal weight were observed with dietary exposure to 100 ppm or less of Aroclor 1254 for 90 days premating through gestation (Welsch, 1985). A single dose of 244 mg/kg Aroclor 1254 was reported in one study to be associated with hydronephrosis of unknown significance, but this dose had no effect on fetal weight or incidence of cleft palate (Haake et al., 1987). In another study, Kanechlor 500 was administered in dosages ranging from 36 to 364 mg/kg/day on days 6-15 of gestation (Watanabe and Sugahara, 1981). Statistical significance was not reported for the data, but it appears that 72 mg/kg/day is a LOAEL for terata and resorptions while 36 mg/kg/day is a NOAEL. Since the lowest repeated dosage yielding a positive finding was 72 mg/kg/day in the Watanabe and Sugahara (1981) study, this value is identified as a LOAEL. The 36 mg/kg/day dosage from this study is considered the NOAEL.

NOAEL: 36,000 µg/kg/day
LOAEL: 72,000 µg/kg/day

Rats: Reproductive- Dietary exposures up to 70 ppm Aroclor 1254 have been found to have no effect on conception rate and litter size (Linder et al., 1974; Baker et al., 1977; Spencer, 1982). Rats fed 100 ppm Aroclor 1254 in the diet had a decreased average fetal weight per litter, but no abnormalities in number of implantations or fetal survival rate at birth (Spencer, 1982). In some studies, higher equivalent exposures also had effects on female reproduction (Villenueve et al., 1971a; Sager, 1983; Brezner et al., 1984; Sager et al., 1987). Male reproduction in rats is remarkably resistant to effects of 54% chlorine PCBs. One study found no effect on testes weight in rats fed Aroclor 1254 for 3 weeks in dosages up to 500 ppm (Garthoff et al., 1978), and another found normal spermatogenesis and testicular histopathology after 50 mg/kg/day Aroclor 1254 for 7 days (Dikshith et al., 1975).

Even higher exposures to Clophen A50 (160 mg/kg/day for 3-5 weeks during puberty) had no effect on plasma testosterone or testes weight (Johansson, 1987). These data indicate a NOAEL equivalent to 70 ppm (7 mg/kg/day) and a LOAEL equivalent to dietary intake at 100 ppm (from the Linder et al., 1974 study), or 10 mg/kg/day.

NOAEL: 7,000 µg/kg/day.
LOAEL: 10,000 µg/kg/day

Developmental- One study found no terata accompanying dietary exposure to Aroclor 1254 at levels up to 269 ppm (Overmann et al., 1987). At 269 ppm, there were also no effects on length of gestation or the number of live or dead pups at birth, but pup weight and pup survival were diminished. Some neurobehavioral effects were noted in pups from dams fed 26 ppm. In a three-generation study, chronic dietary exposure of Aroclor 1254 of 20 ppm or less had no effect on litter size or pup weight at weaning (Linder et al., 1974). At 100 ppm, no effects were observed for exposures up to 67 days, but exposures from 129-274 days were associated with decreases in litter size and pup survival at weaning (Linder et al., 1974). In shorter term exposures, 50 mg/kg/day for days 7-15 of gestation caused no terata or effects on litter size (Linder et al., 1974). Exposure at 100 mg/kg/day on days 7-15 of gestation also produced no terata, but pup survival to weaning was decreased. Based upon the neurobehavioral data from offspring in the Overmann et al. (1987) study, a LOAEL equivalent to dietary intake at 26 ppm, or 2.6 mg/kg/day is calculated. From the Linder et al. (1974) study, a NOAEL of 20 ppm, or 2.0 mg/kg/day is derived.

NOAEL: 2,000 µg/kg/day
LOAEL: 2,600 µg/kg/day

Rabbits: Reproductive- In one study, Aroclor 1254 at a dosage of 10 mg/kg/day for 28 days had no effect on conception rate, number of viable fetuses, resorption rate, or abortion rate (Villenueve et al., 1971a&b). At 12.5 mg/kg/day or greater for the same interval, conception rates were decreased, and there was an increased rate of resorption and fetal death. In another study, the administration of 300 mg/week of Aroclor 1254 for 14 weeks resulted in uterine atrophy (Koller and

Zinkl, 1973).

NOAEL: 10,000 µg/kg/day
LOAEL: 12,500 µg/kg/day

Developmental- No effect on fetal weight was observed with exposure to Aroclor 1254 at 10 mg/kg/day for 28 days (Villenueve et al., 1971a&b). However, at dosages of 12.5 mg/kg/day and above there were increased abortions, stillbirths, and resorptions (see Reproductive, above).

NOAEL: 10,000 µg/kg/day
LOAEL: 12,500 µg/kg/day

Monkeys: Reproductive and Developmental- Pregnant cynomolgous monkeys were exposed to 100 or 400 µg/kg/day beginning after approximately 60 days of gestation in a study by Truelove et al. (1982). The two monkeys treated with 100 µg/kg/day each delivered a dead, term, male offspring. The single monkey treated with 400 µg/kg/day delivered a normal, term, female offspring. The absence of apparent dose-response relationship and the small number of animals make it impossible to establish a NOAEL or LOAEL .

2.1.7 Other Sensitive Tissues, Sensitive Species, or Commercial Mixtures

The above analysis was restricted to toxicity information for 42% and 54% chlorine PCBs in order to estimate ADIs for these commercial mixtures. The five most studied specific target organs/tissues were evaluated in the four most commonly employed laboratory animal species. In order to insure that this approach did not bias the outcome by overlooking some other potentially sensitive target organ toxicity in these or other species, literature covering other toxic endpoints for PCBs in all species was reviewed. Also, observations with commercial mixtures other than 42% and 54% chlorine content were examined. The results of this review are summarized below.

2.1.7.1 Other Species

Among species other than those included in the above analysis, the mink appears to be the most sensitive to PCB toxicity. The median lethal concentration of 54% chlorine PCBs in the diet for mink has been estimated to be about 80 ppm for a 28-day exposure and only 6.65 ppm for a 280-day exposure (Bleavins et al., 1980; Hornshaw et al., 1986). Reproductive failure and some mortality have been observed with dietary exposure to 2 ppm (Aulerich and Ringer, 1977) or 2.5 ppm Aroclor 1254 (Aulerich et al., 1985). No adverse effects on reproduction or mortality attributable to PCBs were seen with 1 ppm dietary exposure of mink to Aroclor 1254 for five months (Aulerich and Ringer, 1977). Information on toxic endpoints other than reproductive/developmental and mortality is lacking. These observations suggest a steep dose-response relationship, with a NOAEL at 1 ppm and an LOAEL of 2 ppm. The authors indicated that the mink fed 2 ppm consumed 61 mg of PCBs over a nine month period. Assuming that the mink weigh approximately 1 kg as described in the paper, the average daily PCB dose corresponding to 2 ppm in the diet would be 225 μg/kg/day. A 2 ppm dietary exposure to Aroclor 1242 resulted in the same incidence of mortality as 2 ppm Aroclor 1254, 12%, indicating that this mixture is about equally toxic. A 225 μg/kg/day LOAEL for mink for both 42% and 54% chlorine PCBs indicates that mink have a sensitivity to PCB toxicity similar to that of the monkey.

Limited studies of 54% chlorine PCB toxicity have been conducted using guinea pigs or Yorkshire pigs (Miniats et al., 1978; Brunstroem et al., 1982). These studies found either no effect or effects at dosages well above the LOAELs for other species.

2.1.7.2 Other Tissues

While PCBs have been reported to have effects on tissues other than those included in the analysis above, none of these other tissues appear to be more sensitive to PCB toxicity. For example, Garthoff et al. (1977) found evidence of kidney injury in the form of elevated blood urea nitrogen levels among rats treated for 2-5 weeks with Aroclor 1254 at dietary levels from 50 to 500 ppm. However, in this same study, hepatic effects were observed at dosages one-tenth the lowest

dosage associated with possible kidney injury.

A number of studies have reported altered serum lipid levels with 54% chlorine PCB treatments. The lowest dosage found to increase serum cholesterol in rats was 8 ppm Aroclor 1254 in the diet for four days, corresponding approximately to a LOAEL of 800 μg/kg/day (Carter, 1984; 1985). A lesser dosage equivalent to approximately 400 μg/kg/day had no effect. Similar results were obtained in another study with Clophen A-50 in which a dosage of roughly 570 μg/kg/day in rats had no effect on cholesterol (Baumann et al., 1983). Triglycerides were also found to be increased when dosages equivalent to roughly 14.3 mg/kg/day or greater were administered (Baumann et al., 1983). Higher dosages of 54% chlorine PCBs have been observed to result in altered serum cholesterol and triglycerides in rats and rabbits in other studies, although in some studies a decrease rather than an increase is noted (Kling et al., 1978; Oishi et al., 1978; Garthoff et al., 1977; Allen and Abrahamson, 1973: Koller and Zinkl, 1973; Allen et al., 1976; Zinkl, 1977; Yagi and Itokawa, 1980). The absence of effects on serum lipids at dosages around 500 μg/kg/day, which is the LOAEL for toxic effects of 54% chlorine PCBs on the liver and thyroid, indicates that serum lipid metabolism is not the most sensitive target site for PCB toxicity.

Hematologic effects have been noted in some studies, although not consistently. Some studies have found no abnormal hematologic parameters in rats fed 54% chlorine PCBs in the diet at 100 ppm (Oishi et al., 1978; Allen et al., 1976), or in rabbits administered 42% chlorine PCBs at 300 mg/week for 14 weeks (Koller and Zinkl, 1973). Other studies have reported lymphocytopenia (Allen and Abrahamson, 1973), leukocytosis (Becker et al.,1979), increased or decreased hemoglobin concentrations (Allen and Abrahamson, 1973; Becker et al., 1979; Bruckner et al., 1974b), and neutrophilia (Allen and Abrahamson, 1973; Bruckner et al.,1974b) in rats and monkeys fed PCBs. However, in each case in which hematologic abnormalities were reported, these occurred along with other prominent organ/tissue toxicities. The formed elements of the blood do not therefore appear to be especially sensitive to toxic effects of PCBs.

There is no evidence that the nervous system is particularly sensitive to insult from PCBs. While in some cases, PCBs have been observed to affect

neurotransmitter levels in rats, the doses employed in these studies were quite high, e.g. 500 - 1,000 mg/kg (Seegal et al., 1985a; 1985b; 1986). Lesser dosages of 54% chlorine PCBs have been associated with changes in brain dopamine and norepinephrine in ring doves, but these dosages (10 or 100 ppm in the diet) also produced generalized toxicity in the animals (Heinz et al., 1980). Neurobehavioral deficits have been noted in offspring from rats and monkeys fed PCBs (e.g. Bowman et al., 1981; Overmann et al., 1987). These have been considered in the above analysis under developmental effects.

2.1.7.3 Other PCB Mixtures

Toxicity data are available for commercial PCB mixtures with 21, 41, 42, 48, 54, and 60% chlorine content. The mixtures with the most data available are 42% and 54% chlorine PCBs, and these mixtures have been included in the analysis. Relatively few studies have been performed using 21% chlorine PCB mixtures, and they indicate that these mixtures are among the least toxic. PCB mixtures with 60% chlorine content have been studied more frequently than the 21% chlorine mixtures, but less extensively than 42% and 54% chlorine mixtures. However, the oncogenic effects of 60% chlorine mixtures in animal studies are well established and in the present hazard evaluation will be considered of sufficient weight to obviate consideration of other toxic effects.

PCB mixtures of 41% chlorine content (i.e., Aroclor 1016) have been studied to a limited extent, and the lowest dosages producing toxicity are found in the two most sensitive species, the mink and monkey. Mink experienced mortality and reproductive effects when fed Aroclor 1016 at 20 ppm for eight months. Since only one dosage was tested in this study, no NOAEL could be identified. Barsotti and van Miller (1984) fed female rhesus monkeys diets with 0.005, 0.164, and 0.7 ppm Aroclor 1016 for 87 $\pm$ 9 weeks. Hematologic and clinical chemistry values for the Aroclor 1016-treated monkeys were normal. Each female bred to an untreated male conceived and delivered normally. Offspring from monkeys fed the higher dosage (0.7 ppm) had a small but statistically significant decrease in body weight at birth, but no difference in stature (head circumference and crown to rump length). No difference in body weights were noted at weaning. This study provides insufficient evidence for adverse effects to designate it as a LOAEL;

rather it will be considered to represent a NOAEL for this mixture in this species.

Very little data is available with which to evaluate the relative toxic potency of 48% chlorine PCB mixtures. The few studies in the literature for this mixture have been conducted primarily in monkeys, and information with which to compare toxicity with other mixtures is sketchy at best. Based upon this limited data base, there is no indication that 48% chlorine PCBs are unusually toxic.

2.1.8 Conclusions

It is apparent from this supplemental review that the mink, like the monkey, is an extraordinarily sensitive species to toxic effects of PCBs. No other unusually sensitive species were identified. While toxicity from PCBs has been observed in tissues not included in the original analysis, in no case was one of these tissues found to be more sensitive (i.e. affected at a lower dosage) than the most sensitive tissue identified in the analysis. Though nononcogenic toxic effects have been reported for all commercial PCB mixtures studied, no PCB mixture could be identified that had significantly greater toxic potency than 42% and 54% chlorine PCBs. Because the toxicities described in the NOAEL/LOAEL analysis in section 2.1.2 are at least equivalent to or exceed those for other species, other PCB mixtures, and other toxic endpoints not included in this analysis, it is unlikely that NOAELs and LOAELs from this analysis will under-represent the toxicity of PCBs in general or that of any specific PCB mixture.

2.2 A Review of the Animal Carcinogenicity Bioassays

Limited data are available for analysis of the potential for 42% chlorine and 54% chlorine PCB mixtures to induce cancer in laboratory animal species (Table 2.1). Many deficiencies are evident in the design of available studies (e.g., too few doses employed, exposure for less than a lifetime, concurrent experimental procedures which impart a promotional aspect, etc.) but results from these studies can be used to provide some evaluation of the potential carcinogenicity of these mixtures.

2.2.1 42% Chlorine PCBs

The carcinogenicity of Kanechlor 300 was investigated in mice during the early 1970s. Male mice of the dd strain were fed diets containing Kanechlor 300 at dietary levels of 100, 250 and 500 ppm for 32 weeks (Nagasaki et al., 1972). Whereas hepatomas were observed in the group treated with higher chlorinated PCB species (Kanechlor 500), mice exposed to Kanechlor 300 were reported to have no hepatomas, nodular areas or necrotic foci. Details in this report were sparse, so it is difficult to evaluate experimental design or histopathologic evaluation.

Subsequent reports of this same study (Ito et al., 1973a&b) gave somewhat greater detail of the study design and histopathologic findings. Liver weight in treated animals was significantly elevated and microscopic examination of the livers revealed focal hypertrophy of centrilobular hepatocytes in the space between the sinus endothelium and the hepatocytes. Female mice treated in this experiment were less responsive to the hepatotoxic effects of Kanechlor 300 and none of the treated female mice suffered from amyloid degeneration in the liver. Like male mice, however, female mice showed evidence of hepatocellular hypertrophy. No neoplastic or pre-neoplastic lesions were observed in any mice treated with any dose of Kanechlor 300.

Kanechlor 300 was administered to male Wistar rats at dietary levels of 100, 500 or 1,000 ppm for 52 weeks by Ito and co-workers (1974). No hepatocellular carcinomas were found in any of the treated rats. At the highest dose, cholangiofibrosis was found in livers examined, but this effect was absent at the lower dosages tested. Hypertrophy of centrilobular cells was not a significant finding in animals treated with Kanechlor 300.

Schaeffer et al. (1984) exposed 152 male Wistar rats to Clophen A 30 over their lifetime at a dietary concentration of 100 ppm. Necropsies were performed on animals which died or were sacrificed in a moribund condition prior to day 801 of the experiment and on animals randomly killed between day 801 and the end of the experiment on day 832. While the incidence of neoplastic nodules was increased by Clophen A30 treatment, the relevance of this finding is severely limited by the fact that these neoplasms had not progressed to benign or

malignant tumors. After 832 days the incidence of hepatocellular carcinoma was 2% in the control (unexposed) group and 3% in the Clophen A30 group; a nonsignificant difference. Interestingly, survival to day 801 was significantly greater in the treated group compared to control, perhaps due in part to the fact that PCB treatment had significantly decreased the total tumor load in the animals over the course of the experiment.

These data do not indicate a carcinogenic potential for 42% chlorine mixtures in mice or rats. However, several of the studies used less than lifetime exposure regimens. This shortcoming limits their usefulness, particularly as development of rat liver tumors with 60% mixtures has been shown to be a phenomenon that is encountered late in the life of the animal. An experiment with rats, however, was of sufficient duration and was consistent with all other studies in that tumor development was not found (Schaeffer et al., 1984). For animals treated with Kanechlor 300, nodular hyperplasia or hepatomas were not consistently found indicating that even if large doses are administered for 30% to 50% of the animal's lifetime, conditions presaging development of malignant cancers are not observed.

2.2.2 54% Chlorine PCBs

Groups of male BALB/cJ mice were fed Aroclor 1254 at a dietary level of 300 ppm for six months followed by a five-month recovery period or 300 ppm continuously for eleven months (Kimbrough and Linder, 1974). Mortality in the PCB-treated groups apparently was high during the first four months; however, this was not related to treatment since control animals exhibited a similar incidence of mortality. Hepatomegaly and cholangiofibrosis were consistent findings in the group treated for eleven months; some of the livers exhibited extensive necrosis and fibrosis. For the 22 mice surviving this treatment regimen, ten hepatomas (benign liver lesions) were found in nine livers. No hepatomas were observed in the group treated for six months. However, two-thirds of the livers examined had fibrosis, and hepatocellular necrosis was evident in most of the livers.

For the series of reports on PCB carcinogenicity in mice from Japanese

investigators (Nagasaki et al., 1972; Ito et al., 1973a&b; Nagasaki et al., 1974) previously discussed, the carcinogenic potential for Kanechlor 500 was also evaluated. Initially (Nagasaki et al., 1972), it was reported that dietary levels of 100, 250 or 500 ppm Kanechlor 500 administered for 32 weeks to male dd mice produced hepatomas only at 500 ppm (7/12 or 58%). In subsequent publications (Ito et al., 1973a&b), these hepatomas were apparently reclassified as carcinomas. Nodular hyperplasia was then reported in 7/12 animals, and 5/12 of the livers were reported as having well-differentiated hepatocellular carcinomas. In contrast, a lack of tumors in female dd mice exposed to 100, 250 or 500 ppm Kanechlor 500 for 32 weeks was reported by Nagasaki et al. (1974). In fact, few histopathologic changes were observed; the amyloid degeneration commonly found in male mice was absent in similarly treated female mice. The apparent sensitivity of male dd mice to hepatic lesions is not understood and this observation has not been confirmed.

Ito et al. (1974) fed Kanechlor 500 to male Wistar rats at dietary levels of 100, 500 and 1,000 ppm for 52 weeks. No hepatocellular carcinomas were found in the livers of treated rats at any dose tested. Nodular hyperplasia was noted in 30-40% of the rats exposed to Kanechlor 500 at both 500 and 1,000 ppm.

The National Cancer Institute (NCI) reported the results of a bioassay for the carcinogenic potential of Aroclor 1254 in 1978. Groups of 24 male and female Fischer 344 rats were exposed to dietary levels of 25, 50 or 100 ppm Aroclor 1254 over a period of 105 weeks. Decreased body weight (>10%) in the high dose groups was noted. Clinical signs of toxicity including alopecia, darkened urine, facial edema, exophthalmos and cyanosis were noted in the high- and mid-dose groups near the end of the exposure period. Also, decreased survival in male animals showed a significant dose-related trend. The incidence of nodular hyperplasia and adenomas appeared to be dose related, but very few carcinomas were observed at the end of the experiment. Two hepatocellular carcinomas were observed among males in the 100 ppm group, one in the 50 ppm group, and none in the 25 ppm group; no liver tumors were found in the females at the dose levels tested. NCI concluded Aroclor 1254 was not carcinogenic for the Fischer 344 rat.

Sections of frozen tissues from the NCI bioassay were re-analyzed by Ward and coworkers. Morgan et al. (1981) re-evaluated stomach samples which had been stained for alkaline phosphatase and re-sectioned. The authors noted that intestinal metaplasia (which was not apparent in animals dying before the 73rd week) was related to dose. These stomach lesions were not found to be related to liver lesions previously described. Gastric adenocarcinomas were found (6 of the 33 lesions observed) but incidence did not appear to be related to dose. The authors concluded that exposure to Aroclor 1254 leads to induction of intestinal metaplasia and probably leads to adenocarcinoma of the glandular stomach.

Ward (1985) re-evaluated slides originating from the NCI study and reclassified liver lesions according to a slightly different scheme than that used by the NCI in its original report. By reclassifying nodular hyperplastic lesions as adenomas if there was compression on two sides of the focus, Ward suggested that 8/72 male rats exposed to Aroclor 1254 had adenomas and that these lesions were related to dose. The types of hepatocellular adenoma found varied and were histopathologically described as either eosinophilic, basophilic, or vacuolated adenomas, but the predominant type observed by Ward was clearly eosinophilic adenomas. As Ward notes, PCBs are inducing agents and cause a proliferation of smooth endoplasmic reticulum, an effect which causes the affected hepatocyte cytoplasm to appear eosinophilic. Thus, the slight increase in liver adenomas (benign tumors) may have been the result of a very weak promotional effect. Ward described only two hepatocellular carcinomas (one less than found by NCI); both were observed in males of the highest exposure group, an increase not significantly different from control. In female rats Ward reported no carcinomas and a nonsignificant increase in eosinophilic adenomas unrelated to dose. The lack of any trend with dose in female rats (even though the finding of three eosinophilic adenomas observed in the 50 ppm female group was equivalent to the three eosinophilic adenomas in the 100 ppm group) raises questions as to whether or not the weak trend suggested for the results in the male animals was coincidental rather than real. Given the shortcomings inherent to the original NCI study and this re-evaluation by Ward, the findings of Ward are considered equivocal evidence at best.

Table 2.1
Summary of Carcinogenicity Bioassays for Various PCB Mixtures

Reference	Commercial Mixture	Dosage in food (ppm)	Exposure Period	Result
42% Chlorine PCB Mixtures				
Mice:				
Ito et al., 1973a&b	Kanechlor 300	100 250 500	32 wks	No evidence
Rats:				
Ito et al., 1974	Kanechlor 300	100 500 1000	52 wks	No evidence
Schaeffer et al., 1984	Clophen A30	100	832 days	Negative
54% Chlorine PCB Mixtures				
Mice:				
Ito et al., 1973a&b	Kanechlor 500	100 250 500	32 wks	Positive
Kimbrough& Linder, 1974	Aroclor 1254	300	6 mo 11 mo	Negative
Rats:				
NCI, 1978	Aroclor 1254	25 50 100	104-105 wks	Negative
Ito et al., 1974	Kanechlor 500	100 500 1000	52 wks	Negative

Table 2.1 (continued)

Reference	Commercial Mixture	Dosage in food (ppm)	Exposure Period	Result
60% Chlorine PCB Mixtures				
Rats:				
Kimbrough et al., 1975	Aroclor 1260	100	21 mo	Positive
Schaeffer et al., 1984	Clophen A60	100	832 days	Positive
Norback & Weltman, 1985	Aroclor 1260	100 ppm for 16 mo, then 50 ppm for 8 mo, sacrifice at 29 mo		Positive

2.2.3 60% Chlorine PCBs

Kimbrough et al. (1975) investigated the oncogenic potential for Aroclor 1260 and reported the first positive finding for this PCB mixture. Female Sherman rats were exposed to Aroclor 1260 at a dietary level of 100 ppm for approximately 21 months. Weight loss within the exposed group was less than 10%, indicating that the maximally tolerated dose had not been exceeded during the course of the study. Significant increases in neoplastic nodules (144/182) and carcinomas (26/184) were noted in livers of exposed animals at necropsy. Total tumor load in exposed animals (73%) was slightly less than that observed in control animals (78%); extrahepatic tumor load was also less (60% *vs.* 77%). Thus, although there was a significant elevation of hepatic tumors in the exposed group compared to control, the increase was offset by decreased incidence of tumor at other sites. Survival in the exposed group was better than control; approximately twice as many control animals died prior to termination of the experiment.

The effects of Clophen A60 on Wistar rats were studied in an experiment which was conducted over a period approximating the natural life span of the rat (Schaeffer et al., 1984). Weanling male Wistar rats were exposed to 100 ppm Clophen A60 in their diet for a period of up to 832 days (118 weeks, 6 days). Animals dying prior to day 800 were necropsied, and starting on day 801 the remaining animals in the study were randomly selected and necropsied. This process was completed on day 832 of the experiment. Of the exposed animals dying prior to day 800, 9/44 were found to have hepatocellular carcinomas (a statistically significant increase); this lesion did not appear prior to day 700. Mortality in the exposed group was significantly less than control and the incidence of thymoma and other neoplasms was also significantly reduced compared to control. Animals surviving past day 800 showed significant increases in hepatocellular carcinomas and, as in the Kimbrough et al. (1975) study, were found to have lowered incidences of extrahepatic tumors.

Interestingly, data from the Schaeffer et al. study demonstrate that progression of liver lesions to the carcinoma stage is a phenomenon of later life. Of animals necropsied in the 701-800 and 801-832 day time periods, 30% and 61%, respectively, were found to have hepatocellular carcinoma. Prior to these time

periods the incidence was reported to be 0%.

The third study which described oncogenic potential for 60% chlorine mixtures was reported by Norback and Weitman (1985). In their protocol, male and female Sprague-Dawley rats (group size was 70 each) were fed 100 ppm Aroclor 1254 for 16 months; the dose was then reduced to 50 ppm for the ensuing 8 months, and finally, the experimental animals were given a PCB-free diet for the last five months of the experiment. The estimated average dose over the course of the experiment was approximately 69 ppm. Partial hepatectomies were performed on two controls and three PCB-exposed animals of each sex at the 1, 3, 6, 9, 12, 15, and 18 month time periods. At 24 months a similar group (two controls and three treated rats) was sacrificed and necropsied, and all remaining animals were killed and necropsied at the 29 month terminus of the experiment. Trabecular carcinomas (19/47) and adenocarcinomas (24/47) were significant findings in female animals exposed to Aroclor 1260. A strong sex-dependent incidence of these lesions was noted in the study since only 2/46 males were reported to have hepatocellular carcinoma, and adenocarcinoma was not found in the males. Like the Schaeffer et al. (1984) study, development of carcinomas occurred late in life for the exposed animals. Trabecular carcinomas were not observed before 15 months, and adenocarcinomas did not appear before the 24-month sacrifice. Overall, 79% of the tumors observed were seen at the 29 month sacrifice. Although this study confirms data presented in earlier reported studies, the promotional effect of partial hepatectomy and the sharp sex-dependent differences confound its interpretation and use in the risk assessment process.

A recent paper (Rao and Banerji, 1988) reported that neoplastic nodules can be induced in rat liver following an exposure period as short as 120 days. Male Wistar rats, 32 per group, were fed Aroclor 1260 at dietary concentration of 0, 50, or 100 ppm. No carcinomas were observed after the 120-day exposure period, although the authors did report increases in neoplastic nodules which were inversely related to dose. The absence of a coherent dose-response relationship makes the results of this study difficult to interpret. This, and the absence of carcinoma as an endpoint, make these results unsuitable for use in making cancer potency estimations. While the study shows that neoplastic nodules

appear within a relatively short time in Wistar rats treated with Aroclor 1260, the study of Schaeffer et al. (1984) in the same strain clearly indicates that with continuing lifetime exposure these nodules will not progress to carcinomas until very late in the life of the animal.

2.3 A Review of the Human Health Effects Observed in Occupational Studies and Related Exposure Levels

2.3.1 Human Occupational Studies - General Clinical Findings

Two recent reviews have summarized the evidence provided by the various clinical studies in occupationally exposed workers. The findings of these reviews are noteworthy and will be reiterated here (Brown et al., 1981; Gaffey, 1981). First, while higher exposures to PCBs tend to mean a higher body burden, there was a general lack of correlation between exposure duration and body burden. Second, although not all studies agree, there was an indication that the PCBs of higher chlorine content were more likely to accumulate in adipose tissue, suggesting a slower metabolism rate. Third, the general health of the occupationally exposed group was considered to be good.

Gaffey (1981) summarized the results of 17 epidemiological studies of health effects of PCBs. While clinical details were not provided in two of these studies, both concluded that the workers were in good health despite high exposures (up to 1900 ppb blood PCB levels were reported in one of these studies). Of 15 studies reporting clinical measurements, 11 reported dermatologic effects, nine reported liver function tests, six reported lipid measurements, and five reported on blood chemistry. Gaffey concluded that while no clear correlation between PCB blood levels and chloracne was provided, the studies suggested that when PCB blood levels exceed 150 to 200 ppb, chloracne might occur. He also concluded that dermatitis, like chloracne, was a frequently observed effect, and that it might be associated with the body levels of the higher chlorine content PCB compounds. Of the nine reported studies of liver function, only five found some mild change in liver function tests. No consistent pattern was identified, nor was an association between these changes and PCB blood levels ever found. No adverse health effect was associated with PCB exposure in any of the studies. In the six studies in which lipid metabolism was considered, the most consistent change observed was

an elevation in serum triglyceride. However, as Emmett (1985) has observed, this may reflect an influence of triglycerides on PCB partitioning rather than an effect by PCBs on lipid metabolism. Of the five studies of blood chemistry, none reported any relationship between the tests and PCB biood levels. Of the two studies that measured blood pressure, one found no association while one reported an association between PCB levels and diastolic blood pressure (Gaffey, 1981).

The appearance of histopathologic lesions in the livers of laboratory animals exposed to PCBs has generated considerable concern that PCBs may be hepatotoxic in man. Many of the clinical biochemical parameters incorporated into the epidemiological studies described above were specifically for the purpose of assessing PCB effects on liver function, and the results of these tests call for some additional comment. A number of studies noted statistically significant changes in indices of liver function, but the magnitudes of these changes were uniformly quite small. Small changes in these parameters can reflect other physiologic processes besides toxicity. For example, there is evidence that serum transaminase activities, e.g. SGGT, and serum triglycerides may be increased during enzyme induction (Whitfield et al., 1972; Martin et al., 1975; Emmett, 1985; Guzelian, 1985). PCBs have been shown to cause hepatic enzyme induction in both laboratory animals and in occupationally-exposed workers (Alvares et al., 1977). Other common exposures, e.g. alcohol consumption, can also produce mild changes in these parameters (Guzelian, 1985). Therefore, while substantial, consistent alterations in the parameters used to evaluate liver function would clearly indicate liver injury, the minor changes and inconsistent patterns observed after PCB exposure cannot be concluded to be a consequence of hepatotoxicity (Emmett, 1985; Guzelian, 1985).

Of interest to the interpretation of occupational exposure studies is the Rosenberg et al. (1987) analysis of the validity of self reported occupational histories in PCB-exposed workers. Worker recall of job history related to PCB exposure was compared to company records and "validity" was indexed according to worker age, duration of employment, diversity of jobs, worker sex, and interviewer. Mean nonvalidity was 25% with considerable variability, and the only independent predictor of validity was job diversity (not surprisingly, fewer jobs per individual correlated with higher validity). The authors concluded that

self reporting may have fallen short of what was necessary to ensure dependable relative risk estimates for PCB exposure. Such a finding has relevance to occupational and epidemiological studies which attempt to assess previous chemical exposures by personal interviews. Persons with short employment duration and/or high job diversity may confound the results of mortality and other comparisons because these job characteristics are poorly correlated with self-reported exposure validity as illustrated by Rosenberg et al. (1987).

The highest and longest PCB exposures to humans have occurred in the occupational setting. Serum PCB concentrations in workers roughly 100 times those observed in the general population have been reported. The study of these workers probably represents the best opportunity for determining adverse health effects of PCBs in humans. Several cohorts of occupationally exposed workers have been examined for the presence or history of physical illness and have been subjected to a variety of clinical laboratory measurements. The only physical symptoms that could be conclusively attributed to PCBs were chloracne and other dermatological lesions in workers exposed to high levels of PCBs. One study (Warshaw et al., 1979) reported diminished respiratory function, but groups were poorly matched for the important variable of smoking status, and the results of a longitudinal study of this population indicated that the initial findings were artifactual due to test operator inexperience and inadequate expiratory effort (Lawton et al., 1986). Several studies have used clinical laboratory tests to measure liver function status in PCB-exposed workers. The results were generally negative, and when changes were noted they were uniformly small and of questionable clinical relevance. Further, changes in one clinical test of liver function were generally not supported by other measurements of liver function in the same study. Such minor and inconsistent abnormalities would be anticipated in any large study of a healthy population, and the data therefore do not indicate clinical hepatotoxicity with PCB exposure in workers. Elevated triglycerides were associated with serum PCB levels in some studies, and it has been suggested that PCBs alter lipid metabolism. However, studies of the distribution of PCBs indicate a greater solubility of PCBs in serum with a higher lipid content. As a consequence, elevated triglycerides cause a greater percentage of an individual's PCB body burden to appear in the blood. The association between serum PCB levels and triglycerides therefore results from the influence of triglycerides on

serum PCB levels rather than the reverse. In conclusion, a review of the human data from studies of occupationally exposed persons, while demonstrating that PCBs caused dermal problems, failed to identify any significant clinical disease associated with electrical grade PCBs (Fischbein et al., 1979; Smith et al., 1982; Brown et al., 1981; Gaffey, 1981; Drill et al., 1982; Emmett, 1985; Kimbrough, 1987). Even though some physiologic changes were noted, no clinical significance could be attached to any of these changes. For a more detailed summary of these studies see the Toxicant Profile For Polychlorinated Biphenyls (TERRA, 1988).

2.3.2 Human Occupational Studies - General Epidemiological Findings

The data resulting from the mortality studies performed to date have not provided evidence of carcinogenicity in humans from exposure to PCBs. Most of the studies are negative on this point. In each of the studies where positive associations between PCBs and carcinogenicity were suggested, weaknesses in the studies did not permit a causal association to be either proved or dismissed.

When the studies are considered collectively, they do not meet the epidemiologic criteria necessary to establish a causal relationship between PCBs and cancer of any kind. The criteria used in making this determination are: 1) Strength of the association (is the association substantial or marginal?); 2) Consistency of effect (is the same type of cancer uniformly observed in a number of studies?); 3) Temporal relationships (is there a plausible relationship between latency and cancer incidence?); 4) Dose-response relationships (does risk of cancer increase with increasing exposure?); 5) Biological plausibility (is there supporting animal evidence?); and 6) Coherence of the evidence.

The first considerations under these criteria are the strength of the association and the consistency with which it has been demonstrated. For cancer in general, the association can be considered no better than weak. Bertazzi et al. (1981;1987) reported a significant increase in overall cancer rate, but many of these cancers were contributed by individuals with questionable PCB exposure. The much larger studies of Nicholson et al. (1987) and Brown (1987) found no excess in overall cancer rate, and in fact the observed rates were slightly less than expected. Smaller studies by Zack and Musch (1979) and Gustavsson et al. (1986)

also found no increase in cancer rate. The purported associations between PCBs and specific cancer types were for malignant melanoma, cancers of the digestive tract, hematologic cancers, and liver/biliary cancer. Not only do the associations purported in each study differ, but significant limitations are inherent to each purported association. For example, the preliminary report of Bahn et al. (1976) which reported malignant melanomas is confounded by the fact that the cohort studied was exposed to a number of chemicals other than PCBs and the fact that this association was never confirmed in any of the larger studies that followed. Bertazzi et al. (1987) reported a significant excess of GI tract cancers in males and of hematologic cancers in females. These findings are confounded by the facts that: 1) They have not been verified in any other study, 2) The classifications used are overly broad, 3) Each association is sex specific, and 4) When persons of limited exposure are removed from the cohort both associations disappear. Similarly, the reported excess of liver/biliary tumors by Brown (1987) disappears when either tumors of questionable origin are removed or when cancers of short latency or following limited exposure are removed. This latter problem, i.e., the fact that 80% of the cancers in this category were from females in one plant with 1.5 years or less of exposure, is illustrated by the Nicholson et al. (1987) study which found no such associations in persons with much greater exposure and latency periods. Brown states:

> *The update provides limited information ..... The limitations of this study include: (1) possible misclassification of the cause of death, ... it is not clear in every case that the cause of death was due to primary cancer of the liver, gall bladder, and biliary tract; (2) the category of death found in excess includes cancer types that are different from those found in animals exposed to PCBs; and (3) the pattern of risk by latency and duration of employment is not completely consistent with that of an occupational carcinogen, ...*

Given the above limitations, it can only be concluded that no association emerges from these studies, and each purported association is, at best, tenuous.

Temporal and dose-response relationships are clearly not evident in the present epidemiological studies. Bertazzi et al. (1987) concluded that, "Analysis by duration of exposure, latency, and year of first exposure did not reveal any definite pattern or trend of mortality for any of the relevant causes." Brown (1987)

similarly found no clear association between length of employment (as a measure of exposure) and cancer, nor was latency observed. In fact, in both of these cohorts the cancers of most concern were observed in individuals with lesser exposure. This is inconsistent with the dose-response relationship for all chemically induced cancer. Dose-response and latency relationships were also not developed in the cohort studies of Gustavsson et al. (1986) and Nicholson et al. (1987).

With respect to biological plausibility, observations in animals suggest that it is possible for PCBs to produce hepatocellular cancer. Other forms of cancer do not appear to be elevated and may in fact be reduced by PCB exposure. As noted by Brown (1987), the category of death reported to be in excess in each human epidemiologic study is different from that found in animals exposed to PCB, viz., hepatocellular carcinoma. Because of this inconsistency, there is only limited evidence for biological plausibility.

With respect to the criterion of coherence, this condition clearly has not been met. There has been an inconsistency in the reporting of types of cancers elevated between studies and between the types of cancers found elevated in each sex within specific studies. None of the temporal or dose relationships expected for chemical carcinogenicity has been observed in any study.

In conclusion, these six criteria provide a useful framework with which to evaluate the evidence for human carcinogenicity of PCBs provided by mortality studies of occupationally exposed workers. While it might not be reasonable to expect that each of the six criteria be fulfilled before an association is made between an exposure circumstance and a disease (in this case cancer), it is, however, reasonable to expect that most of the criteria are fulfilled before an association is accepted. In the case of PCB exposure and any other specific type of cancer, or cancer in general, only one criterion can be considered met (biological plausibility). And this criterion has only been met to a limited degree. Current evidence, therefore, does not indicate an association between PCB exposure and cancer in humans.

2.3.3 Occupational Exposures - Dose Estimates

2.3.3.1 Dose Estimates Based on Air and Dermal Measurements

Given sufficient exposure information, studies of occupationally exposed persons could provide the most appropriate basis for deriving an allowable level of human exposure to 42% and 54% chlorine PCB mixtures. Although studies of persons exposed to environmental levels of PCBs indicate that exposure to relatively low levels is without clinical effect, the lack of quantitative information regarding PCB exposure precludes the use of these studies in the development of a safe level of intake for 42% and 54% chlorine PCB mixtures. In fact, environmental studies have often evaluated persons with PCB body burdens which are similar to those of the general population. In contrast, based on serum and adipose levels of PCBs, Wolff (1985) estimated that workplace PCB exposures were 10 to 1000 times higher than those of nonoccupationally exposed persons. A list of the reported occupational air exposure levels is provided in Table 2.2 along with a description of the PCB usage and related work activities.

Table 2.2 is comprised of studies reporting air measurements generally taken in the mid to late 1970s as PCB fluids were being phased out of use. Based on more recent literature, and statements made in at least one study (Lawton et al., 1985a), air concentrations in these plants may have been even higher during the 1950s through early 1970s. It is clear from these studies that workers in capacitor manufacturing facilities had greater exposures than did the typical transformer repairman or the utility worker (Smith et al., 1982; Smith and Brown, 1986), and that the typical air exposure of a capacitor worker was several hundred micrograms of PCBs per cubic meter of air or greater. Utilizing data from these studies, estimates of the daily dose of PCBs absorbed via inhalation can be made. Assuming that the amount of air inhaled per eight hour work shift is 10 m^3 (Williams, 1984) and that pulmonary absorption is complete, the following estimated daily PCB doses, as listed in Table 2.3, are derived for the workplace air concentrations reported for capacitor plants.

This calculation indicates occupational exposure to PCB fluids resulted in workers receiving from a one to twelve milligram dose of PCBs each work shift.

The allowable workplace air concentrations, i.e., the Threshold Limit Values (TLVs) set by the American Conference of Governmental Industrial Hygienists and the Permissible Exposure Limits (PELs) set by the Occupational Safety and Health Administration, during this period were 1.0 mg/m^3 for 42% chlorine mixtures and 0.5 mg/m^3 for 54% chlorine mixtures and implied an allowable daily dose of some 5-10 mg/day. While the average exposure during the 1970s appears to have been well below both guidelines, some of the reported measurements (Ouw et al., 1976; Fischbein, 1985) suggest occasional excursions above these guidelines were not uncommon in capacitor impregnation rooms where heated PCB fluids were typically used. Thus, it seems tenable to assume that an average or common daily PCB dose in a capacitor manufacturing plant during the 1950s through mid to late 1970s is reasonably approximated by the geometric mean of the doses listed in Table 2.3, or some 2,705 µg/workday.

Interestingly, it now seems obvious that too little attention was paid to the dermal route of worker exposure. For example, Ouw et al. (1976) neglected to take surface and skin measurements but suggested that the failure of the instituted engineering controls to lower worker PCB blood levels was a result of the high dermal exposures occurring in the capacitor plant which they studied. Recently, Lees et al. (1987) have suggested that both the oral and dermal routes of exposure may have been more important than the respiratory route, particularly when PCBs were used at room temperature. These authors calculated that the dermal exposure from a single drop (0.05 ml) of PCBs spread over the hand would result in an exposure of 54,000 µg/day. Clearly, even limited dermal contact with PCB fluids might easily surpass the inhalation exposure in a capacitor plant or other facility using PCBs.

While the extent of PCB absorption through human skin (dermal bioavailability) is unknown, animal studies in both the guinea pig and monkey have shown that about 34% of the dermally applied PCBs (testing both 42% and 54% chlorine PCB mixtures) was absorbed within 24 hours. Assuming that a conservative figure of 10% would be absorbed in the first eight hours, the dermal dosage resulting from a single drop of technical grade PCB mixtures spread on one's hands would be some 5,400 µg/day.

Some skin measurements have been reported, and these can be used to estimate the magnitude of the dermal dose associated with capacitor manufacture work. In the study of Maroni et al. (1981a), the typical surface contamination in the capacitor plants studied ranged from about 0 4-6.2 $\mu g/cm^2$ (eliminating the one spuriously high measurement of 159 $\mu g/cm^2$), and the corresponding dermal levels ranged from 4-27 $\mu g/cm^2$ in the high-power capacitor department with a mean of 19 $\mu g/cm^2$, and from 2-28 in the low-power capacitor department with a mean level of 10 $\mu g/cm^2$. In the study by Smith et al. (1982), skin smear wipes revealed levels of 0.1-6.7 $\mu g/cm^2$ in the small capacitor facility, and 0.05-4.87 at the private utility company. Table and floor surfaces in the latter facility yielded 8 $\mu g/cm^2$ of PCBs. Both of these studies involved facilities with air concentrations at the lower end of those reported in Table 2.2, probably because these measurements were taken in the early 1980s. Thus, it seems reasonable to assume that the dermal exposure typical of capacitor plants from the 1950s through the 1970s was probably higher.

Still, taking a geometric mean of the two mean values in the Maroni et al. (1981a) study and the comparable, higher levels reported in Smith et al. (1982), one can assume the dermal exposure was probably 8.9 $\mu g/cm^2$ or greater when working around PCB fluids, especially for those individuals working in the capacitor impregnation area where PCB fluids where often heated. Given this mean PCB surface concentration, and assuming that only the face and the hands of these individuals (about 1,000 cm^2) were exposed (a probable underestimate as clothing no doubt became contaminated), the daily dermally absorbed dose becomes 890 μg/day (1,000 cm^2 x 8.9 $\mu g/cm^2$ x 10%/day = 890 μg/day). When this dose is added to the mean inhalation dose previously calculated, the estimated average dose experienced by a capacitor worker is approximately 3,600 μg/day.

2.3.3.2 Dose Estimates Based on Body Burden and Pharmacokinetic Measurements

From the limited number of studies measuring PCB levels in the fat tissue of occupationally exposed persons, Wolff et al. (1982a) and Lawton et al. (1985a) have reported that capacitor workers in the mid 1970s had fat PCB levels ranging above the 400 ppm level with mean fat levels of slightly more than 100 ppm. Although fat levels were not reported in the studies of Maroni et al. (1981) or Ouw et al. (1976), based on their reported mean serum levels and the reported 190:1 fat to serum partitioning ratio for PCBs (Wolff et al, 1982b), the estimated mean fat tissue concentrations in these studies for capacitor workers was also probably

Table 2.2
Occupational PCB Exposures

Study	PCB Mixtures Used at Facility	Comments and Measured Air Concentrations
Ouw et al., 1976	Aroclor 1242	The initial 1974 air concentrations of the capacitor impregnation room were measured in 4 different areas. The reported levels were: 320, 1080, 1440 and 2220 $\mu g/m^3$.
Fischbein et al., 1979	Aroclors 1254, 1242, 1221 & 1016	The air concentrations of the capacitor manufacturing workers were divided into four categories: none (0-70 $\mu g/m^3$), low (71-410 $\mu g/m^3$), medium (411-600 $\mu g/m^3$), and high (600-11,000 $\mu g/m^3$).
Maroni et al., 1981a	French and Italian PCB mixtures of 54% and 42% chlorine content	Plant A workroom air concentrations were measured as: an average of 154 $\mu g/m^3$ (with a range of 80-255) in areas where high power capacitors were made; an average of 193 $\mu g/m^3$ (with a range of 149-275) for areas of low power capacitor assembly; and an average of 59 $\mu g/m^3$ (with a range of 49-70) in the filter department.
Smith et al., 1982	Aroclors 1242 & 1016	The air concentrations at a capacitor manufacturing plant were measured in the capacitor processing and maintenance areas and found to average 81 $\mu g/m^3$ (with a range of 0-264).

Table 2.2 (continued)

Study	PCB Mixtures Used at Facility	Comments and Measured Air Concentrations
Lawton et al., 1985	Aroclors 1254, 1242 & 1016	The authors reported that earlier workroom air concentrations were at least the 690 $\mu g/m^3$ measured in 1976 at these two capacitor plants.
Fischbein, 1985	Aroclors 1254, 1242, 1016 & 1221	This apparent second reporting of the population previously discussed in 1979 lists the mean air concentration as 7 $\mu g/m^3$ in the lowest exposure area and 410 $\mu g/m^3$ in the equipment and quality control areas, while levels of 900 and 11,000 $\mu g/m^3$ were measured in the areas where the capacitors were filled and washed.
Smith and Brown, 1986	PCB mixtures not specified	The mean air concentrations taken from personal monitoring samples were 154 $\mu g/m^3$ for capacitor repairmen, 147 $\mu g/m^3$ for the solderer/hanger, and 127 $\mu g/m^3$ in the miscellaneous assembly areas.
Smith and Brown, 1986	Primarily Aroclors 1254, 1242, 1016	Air measurements taken in the mid to late 1970's ranged from 161-1260 $\mu g/m^3$ in the capacitor impregnation rooms of two small capacitor plants while the maintenance area was reported to be 150 $\mu g/m^3$. In a larger capacitor plant the impregnation rooms ranged from 50-299 $\mu g/m^3$.

Table 2.3

Inhalation PCB Dosages for Capacitor Workers

Study	Mean Air Level ($\mu g/m^3$)	Site	Estimated Daily Dose (μg/day)
Ouw et al., 1976	1265	impregnation room	12,650
Maroni et al., 1981a	154	high power capacitors	1,540
	193	low power capacitors	1,930
Smith et al., 1982	81	capacitor processing and maintenance	810
Fischbein, 1985	410	equipment/quality control areas	4,100
	≥900	impregnation room	9,000
Lawton et al., 1985	690	(area not specified)	6,900
Smith & Brown, 1986	154	capacitor repairmen	1,540
	147	solderers	1,470
	127	misc. assembly	1,270
	710	midrange capacitor plant	7,100
	150	maintenance area	1,500
	175	impregnation room of large capacitor plant	1,750
Arithmetic mean of doses (μg/day):			3,966
Geometric mean of doses (μg/day):			2,705

greater than 100 ppm. In the Lawton et al. (1985) study the authors reported that the mean body weight of the capacitor workers they were studying was 77 kg, of which 22 kg was fat tissue. Thus, these authors estimated the mean PCB body burden to be 2.2 grams. Taking the body burden of the Lawton et al. study (the body burdens for the studies listed above are not likely to have been dramatically different), one can easily derive the daily dose absorbed by these workers knowing the clearance or half-life of PCBs in humans.

Several estimates of the PCB half-life in humans have been reported. Chen et al. (1982) reported the half-lives for two pentachlorobiphenyl congeners to be 6.7 and 9.8 months. Steele et al. (1986) reported that the overall half-life of PCBs more closely resembled the results obtained for the lesser chlorinated PCBs, or approximately 6-7 months. Lawton et al. (1985) estimated the half-life of the lower chlorinated PCBs (approximately 42% chlorine) to be on the order of one year. Last, Jan and Tranik (1988) have reported the elimination of PCBs in environmentally exposed persons, and based on their measurements a half-life of 6-8 months is calculated for PCBs.

Given that these capacitor workers had no doubt achieved steady-state with their long term exposure to PCBs, their daily absorbed dose of PCBs for all routes of exposure can be estimated from the following equation.

$$(1) \qquad \text{Body Burden}_{\text{steady-state}} = \frac{\text{PCB intake (average daily dose)}}{\text{elimination rate constant}}$$

This equation merely states that at steady-state, the amount of PCBs being absorbed each day is equivalent to the amount of PCBs being eliminated each day. The elimination rate can be derived directly from the known half-life of PCBs by the following equation:

$$(2) \qquad \text{elimination rate constant} = \frac{0.693}{\text{half-life}}$$

Using half-lives of 8 months (240 days) and one year to span the range of half-lives reported for PCBs, the elimination rate constant for PCBs must range between 0.00289 days^{-1} and 0.00190 days^{-1}. Using these estimates of the elimination rate constant, and the total body burden of 2.2 grams reported by Lawton et al. (1985), the estimated daily dose absorbed by capacitor workers during the mid 1970s

appears to have ranged from 4,180 to 6,350 µg/day.

2.3.3.3 Summary and Conclusions

Based on measurements of the PCB air concentrations of capacitor plants taken in the mid to late 1970s, when PCBs were being phased out of use, the typical inhalation dose for a capacitor worker, particularly those working in the impregnation areas, was on the order of 2,700 µg/day and occasionally may have been as high as 12,000 µg/day or more in some instances. Limiting the exposed surface area of these workers to that of the face and hands, the estimated dermal dose was found to approximate 900 µg/day. Therefore, based on measured dermal and air levels, the average total daily dose appears to have been 3,600 µg/day. This seems to represent a reasonable number as pharmacokinetic-based estimates of the daily dose received by these workers was 4,200 µg/day when the longer estimate of the PCB half-life is used. Therefore, it seems reasonable to conclude that the typical daily dose of PCBs absorbed by a capacitor worker was in the neighborhood of 3,600-4,200 µg/day. This translates into a daily dosage of approximately 50-60 µg/kg/day for those persons working in capacitor manufacturing facilities.

3.0 QUALITATIVE ASSESSMENT OF THE POTENTIAL HAZARDS POSED BY PCB MIXTURES

3.1 Qualitative Assessment of the Nononcogenic Hazards Identified In Animal Studies

3.1.1 Qualitative Assessment of the Nononcogenic Hazards of 42% PCB Mixtures

A number of different systemic and organ toxicities have been identified in animal studies. The predominantly reported findings are: dermatotoxicity (skin), hepatotoxicity (liver), immunotoxicity, and reproductive /developmental problems. Less frequently reported organ toxicities include those of the thyroid, thymus and GI tract. With the exception of dermatotoxicity, human studies have failed to confirm that these other adverse health effects occur in humans at the level of exposure typical of the occupational setting (Kimbrough, 1987; TERRA, 1988). This lack of confirmation in human studies does not necessarily imply that humans are not susceptible to these toxicities. Rather, it indicates that dosages resulting from typical occupational exposures were insufficient to produce toxicity, perhaps an expected finding as this is the intended regulatory purpose of occupational exposure limits. In spite of the absence of demonstrated toxicity (other than chloracne) in humans it seems prudent to assume that qualitatively, the nononcogenic human health hazards are the same as those found in animals. That is, the organ toxicities occurring in animals will occur in humans at some dose higher than those that have been reported. Because it is assumed that the nononcogenic health hazards in humans are qualitatively similar to those found in animals, a major goal of the qualitative assessment is to identify or approximate the threshold dose for all of these toxicities. A determination of the safe dose for the species thought to best mimic the human response will then be used to generate the quantitative assessment.

A review of the NOAELs and LOAELs reported for Aroclor 1242 suggests that the liver is the most sensitive endpoint in the rat (see Table 3.1). Data for Aroclor 1242 (and Aroclor 1254, see Table 3.2) for the other two rodent species tested, the mouse and the rabbit, further suggests that the liver is among the most sensitive target organs in rodent species. On this basis, and the fact that the rat is the most sensitive of the three rodent species when hepatotoxicity is the critical endpoint, the NOAEL for the rat becomes the value of interest when the rodent species are considered. Only a LOAEL (500 μg/kg/day) has been identified for 42% chlorine PCB mixtures in the rat (Bruckner et al., 1974a&b). However, it is noted that the

Table 3.1

Summary of NOAELs/LOAELs from Animal Studies of 42% Chlorine PCB Mixtures.

Target Organ/Tissue Toxicity	Species[a,b] Mouse	Rat	Rabbit	Monkey	Mink
Hepatotoxicity					
NOAEL	5,625	100*	ID	ID	ID
LOAEL	15,000	500	21,400	ID	ID
Dermatotoxicity					
NOAEL	ID	ID	ID	40-90	ID
LOAEL	ID	ID	ID	120-400	ID
Immunotoxicity					
NOAEL	10,000	ID	ID	ID	ID
LOAEL	25,000	ID	21,400	ID	ID
Thyroid toxicity					
NOAEL	ID	2,500	ID	ID	ID
LOAEL	ID	ID	ID	ID	ID
Reproductive toxicity					
NOAEL	ID	30,000	21,000	ID	ID
LOAEL	ID	ID	ID	ID	ID
Developmental toxicity					
NOAEL	ID	100,000	ID	ID	112
LOAEL	ID	ID	ID	ID	225

[a] All values are listed in units of µg/kg/day.

[b] ID = insufficient data to estimate a NOAEL or LOAEL

* Value is estimated from the LOAEL

differential between the LOAEL and NOAEL dosage for hepatotoxicity in mice is 2.7 (15,000/5,625); and that a similar differential for PCB-induced hepatotoxic effects was observed in rabbits fed Aroclor 1254 (LOAEL/NOAEL = 2.3). In fact, Table 3.1 (and 3.2) indicates that where both a LOAEL and a NOAEL are available, the ratio of these levels is generally less than three. The exceptions to this occur in the mouse and involve studies in which the selected doses prevented any comparisons from being made of doses that are closer in magnitude than a factor of ten. Based on these considerations, and the fact that the effects measured in the LOAEL represent a mild hepatotoxic response, a NOAEL for hepatotoxicity in the rat is estimated to be 100 μg/kg/day (i.e., the NOAEL:LOAEL ratio for hepatotoxicity in the rat is no greater than five).

No other species has been studied as extensively as the rodent species, but studies which have been performed in mink and monkeys suggest these two species may be uniquely sensitive to PCBs. In mink, little other than reproductive toxicity has been studied. Mink have been shown to have very steep dose-response relationships for PCB-induced reproductive problems (Aulerich and Ringer, 1977; Bleavins et al., 1980). Nevertheless, a NOAEL of 112 μg/kg/day is reported to be adequately protective for chronic dietary exposure to 42% chlorine PCB mixtures in this species. In the monkey, the other relatively sensitive animal species, only dermatotoxicity has been reported for 42% chlorine mixtures. This NOAEL for these effects is approximately 90 μg/kg/day based on the average dosage tested in the McNulty et al. (1980) study.

While the database of animal toxicity information for 42% chlorine PCB mixtures is somewhat limited, it does reveal three apparently sensitive, species-specific toxic endpoints which might be considered for the quantitative assessment. These three endpoints include mild hepatotoxicity in the rat, systemic and reproductive toxicity in the mink, and dermatotoxicity in the rhesus monkey. All three animal NOAELs identified or estimated from the animal toxicity data available on 42% chlorine PCB mixtures fall within a relatively small dosage range (i.e., 100-, 112- and 90 μg/kg/day, respectively). However, because: 1) The pharmacokinetic and pharmacodynamic data in these species are insufficient for determining which species is most likely to mimic the human response; 2) The three NOAELs under consideration represent essentially equivalent dosages; and 3) Human dosages from occupational exposures were occasionally higher but without adverse effect (see section 2.3); some combination of these three NOAELs is judged to best estimate the threshold or NOAEL for all animal species. The geometric mean of these three values is 100 μg/kg/day, and

this value will be adopted as the NOAEL in animals to be used later in the development of an allowable daily intake for 42% chlorine mixtures in humans.

3.1.2 Qualitative Assessment of the Nononcogenic Hazards of 54% PCB Mixtures

The amount of animal toxicity information available on 54% chlorine PCB mixtures is somewhat greater than that available for 42% chlorine mixtures. It is evident from a review of Table 3.2 that the most sensitive species and most sensitive toxicological endpoints are similar to those observed for 42% chlorine PCB mixtures. Because of limited hepatotoxicity testing for these two PCB mixtures in the rat, the available data provide the same LOAEL value for each mixture. A LOAEL of 500 μg/kg/day has been suggested in three studies (Linder et al., 1975; Kasza et al., 1978a; Garthoff et al., 1977) while a higher LOAEL was reported in one study (Keplinger et al., 1971), perhaps the result of strain-related differences in response to 54% chlorine PCB mixtures. For reasons similar to those given in section 3.1.1, the NOAEL will be estimated from the LOAEL. However, since studies suggest that overall 54% chlorine mixtures are more potent, a larger conversion factor of 10 will be used. The estimated NOAEL is 50 μg/kg/day.

As already discussed, mink are a particularly sensitive species. In mink, 54% chlorine PCB mixtures exhibit a LOAEL of 225 μg/kg/day and a NOAEL of 112 μg/kg/day for reproductive toxicity (Aulerich and Ringer, 1977). While 54% PCBs are more toxic to mink than 42% PCBs, the use of similar dosage regimens in the animal tests performed prevents the quantitative delineation of these differences (i.e., whether or not they are secondary to systemic effects seen in this PCB-sensitive animal model). Apparently no information on mink toxicity for 54% chlorine PCB mixtures is available beyond the mortality and reproductive toxicity analyses considered here. In monkeys, one laboratory has reported that rhesus and cynomolgous monkeys develop four different toxicities at the 200 μg/kg/day level (Tryphonas et al., 1984; Tryphonas et al., 1986a&b), with morbidity and mortality occurring at a dose level of 5,000 μg/kg/day. An estimated NOAEL for the monkey will be estimated from this reported LOAEL using a 10-fold conversion factor resulting in a 20 μg/kg/day NOAEL for the monkey.

The available animal toxicity data for 54% chlorine PCB mixtures are somewhat more extensive than that of 42% chlorine PCB mixtures, but similarities are apparent between the two databases in terms of sensitive species and sensitive toxicity endpoints. The data for 54% PCB mixtures do reveal several

Table 3.2

Summary of NOAELs/LOAELs from Animal Studies of 54% Chlorine PCB Mixtures

Target Organ/Tissue Toxicity	Species[a,b] Mouse	Rat	Rabbit	Monkey	Mink
Hepatotoxicity					
NOAEL	562	ID	600	ID	ID
LOAEL	5,620	500	1,370	200	ID
Dermatotoxicity					
NOAEL	ID	ID	ID	ID	ID
LOAEL	30,000	1,000	ID	200	ID
Immunotoxicity					
NOAEL	ID	ID	600	ID	ID
LOAEL	15,000	5,000	1,370	200	ID
Thyroid toxicity					
NOAEL	ID	ID	ID	ID	ID
LOAEL	ID	500	ID	200	ID
Reproductive toxicity					
NOAEL	1,500	7,000	10,000	ID	ID
LOAEL	15,000	10,000	12,500	ID	ID
Developmental toxicity					
NOAEL	36,000	2,000	10,000	ID	112
LOAEL	72,000	2,600	12,500	ID	225

[a] All values are listed in units of μg/kg/day.

[b] ID = insufficient data to estimate a NOAEL or LOAEL

toxic endpoints in three species which might be considered for the quantitative assessment. However, 1) The pharmacokinetic and pharmaco-dynamic data in these species are insufficient for determining which species are most likely to mimic the human response; and 2) Human dosages from occupational exposures were often higher but without adverse effect (see section 2.3). Given these facts, some mean value of these NOAELs seems the most reasonable surrogate number. The three animal NOAELs considered here are 50 μg/kg/day for hepatotoxicity in the rat, 112 μg/kg/day for systemic and reproductive toxicity in the mink, and 20 μg/kg/day for systemic toxicity in the rhesus monkey. The geometric mean of these three values is 48 μg/kg/day, and this value will be adopted as the NOAEL in animals to be used in the development of an allowable daily intake for 54% chlorine mixtures in humans.

3.2 Qualitative Assessment of the Carcinogenicity of PCB Mixtures

3.2.1 Qualitative Assessment of the Carcinogenicity of 42% PCB Mixtures

Experiments to evaluate the carcinogenic potential of 42% chlorine PCBs have been conducted in mice and rats in at least three separate studies. Both the rat and mouse studies performed by Ito and coworkers were negative but involved an exposure duration that was less than the lifespan of the experimental animal. However, the rat bioassay study performed by Schaeffer et al. (1984) did utilize an exposure duration that exceeded the two year interval recommended by the National Cancer Institute, and the results of this study did confirm the absence of cancer reported in the previous two studies by Ito and coworkers. Although an increased incidence of neoplastic nodules was reported in this study, there was no evidence of progression after a lifetime of exposure. Additionally, the study conducted by Schaeffer et al. (1984) showed that survival was greater in the PCB exposed group and the incidence of thymomas and other neoplasias was significantly reduced compared to control for those animals examined prior to day 801.

It is apparent, then, that no data indicate that lifetime exposure to 42% chlorine PCB mixtures leads to a significantly enhanced rate of cancer for any tissue in mice or rats. Therefore, this qualitative assessment of the human relevance of these animal studies leads inevitably to the conclusion that 42% PCBs are not carcinogens based on the animal data.

3.2.2 General Considerations Concerning the Qualitative Carcinogenic Hazard of 54% Chlorine PCB Mixtures

A number of important considerations emerge in attempting to interpret the human relevance of animal carcinogenicity data for 54% chlorine PCB mixtures. These include: 1) The steep dose-response curve of the tumorigenic response, 2) The sex dependence of the tumorigenic response, 3) The species dependence of the tumorigenic response, 4) The variability in the classification of the tumorigenic response, and 5) The observation of increased liver tumors in mice only at hepatotoxic dosages and the lack of demonstrated genotoxicity of 54% chlorine PCB mixtures.

3.2.2.1 The Steep Dose-Response Curve for Induced Mouse Liver Tumors

In studies where varying doses of 54% chlorine PCBs were tested and significant increases in tumors were observed, there was a clear relationship between the dose of PCBs and tumor incidence. In separate studies, dietary levels of 100 or 250 ppm given for 6 to 8 months produced no hepatic tumors while 300 to 500 ppm diets, given for 8 to 11 months, were associated with approximately a 40% incidence of tumors. The striking difference in response between mice fed 250 ppm or less, and 300 ppm or greater, suggests the tumorigenesis mechanism possesses a threshold. In support of this suggestion, a comparison of the liver pathology reported for mice in the 250 and 500 ppm groups of the various Ito and coworker studies (see Table 2.1) indicates different results for the two dose levels (i.e., the carcinomas and nodular hyperplasia incidence increases from 0% up to 41-53%) although the dose only differs by a factor of two. Thus, the dose-response curve for all histopathological changes in the liver is very steep, and the appearance of tumors corresponds to definite differences in the degree of hepatic injury.

3.2.2.2 Sex Dependence of the Mouse Liver Tumors

The positive tumor data in the mouse for Kanechlor 500 also demonstrated sex specificity. Despite an approximate 40% incidence of tumors reported as hepatocellular carcinomas in male mice fed 500 ppm Kanechlor 500, no hepatocellular carcinomas were observed in female mice in any treatment group.

However, as noted in the following section, this may relate to the generally higher background incidence of liver tumors in male rodents, especially male mice.

3.2.2.3 Species Dependence in Carcinogenic Response and Determining the Most Appropriate Animal Model

The positive responses seen in male mice were not duplicated in male or female rats, despite treatment of the rats with feeding levels causing significant morbidity, weight loss, and even mortality (as reported in the NCI bioassay). In a shorter study, no liver tumors were observed in either male or female rats even though 1) The highest dose tested in rats (1,000 ppm) was twice that used by the same investigators in mice (500 ppm), and 2) The exposure interval in the rat study was at least 50% longer than that used for mice. Given this disparity in exposure regimen and the fact that the same laboratory observed a 40% carcinoma incidence in mice and no carcinomas in rats, it is obvious that mice are a much more susceptible species. This clearly negative response in rats, in spite of utilizing test conditions more favorable to the development of tumors, raises concern about which animal model is more appropriate for predicting the human response. Is it more appropriate to choose the mouse model simply because it proved positive for carcinogenic response, or are there valid reasons to suspect the mouse data and deem the rat data more appropriate for predicting the human response? This question is addressed in following paragraphs and also in the epidemiology section of this document.

For the purpose of extrapolating animal carcinogenicity data to humans, results from chronic bioassays in which mouse liver tumors are the only evidence of carcinogenicity are typically viewed as providing only questionable or limited evidence of that chemical's carcinogenic potential in man. The relevance of mouse liver tumors in assessing the human risks from exposure to 54% chlorine PCB mixtures must be considered questionable for two primary reasons. First, the spontaneous liver tumor incidence in mice is very high when compared to the incidence of liver tumors in rats or humans (Table 3.3). The mouse liver tumor incidence is some 1,000 to 100,000 times higher than the background incidence of liver tumors in Americans and is 100 times that found in rats. Second, the incidence of spontaneous liver tumors in mice is greatly affected by diet. Manipulation of mouse diets has been shown to lower the incidence of spontaneous liver tumors in mice from 55% to 15% (Nutrition Foundation, 1983).

These data indicate that mouse liver tumor incidence may be profoundly influenced by factors other than the test chemical. Thus, mouse cancer bioassays which are positive for liver tumors are insufficient evidence upon which to classify a chemical as carcinogenic in the absence of supporting data in other species.

Table 3.3

Species Dependence of Spontaneous Liver Tumor Incidence

Species	Range of Incidences	Reference
Americans[1]	0.0012 to 0.0052%	Nutrition Foundation, 1983
Osborne-Mendel Rats	0.2%	Goodman et al., 1980
Fischer 344 Rats	0.4%	Goodman et al., 1979
B6C3F1 Female Mice	3.9%	Ward et al., 1979
B6C3F1 Male Mice	21.6%	Ward et al., 1979
B6C3F1/CrlBR Mice	13.2 to 30.4%	Nutrition Foundation, 1983
Senescent Mice	up to 100%	Nutrition Foundation, 1983

[1]Black and White American liver tumor incidence; range differs slightly by sex.

3.2.2.4 Benign or Truly Malignant Tumors ?

There is some uncertainty in interpreting the results of the chronic bioassays because of the apparent differences in histopathologic criteria used in the evaluation of the lesions observed. Kimbrough and Linder (1974) reported an increased incidence of tumors described as hepatomas. The tumors described in the initial Kanechlor 500 study by Ito and coworkers were first classified as hepatomas, but the authors apparently reclassified them as nodular hyperplasia or hepatocellular carcinoma based upon criteria used for classifying tumors in rats at the time. Whether these tumors reported as carcinomas are in fact truly malignant tumors is unclear, for while no metastases were reported the Ito studies were arbitrarily terminated after eight months. Both benign tumors (adenomas) and malignant tumors (hepatocellular carcinoma) have been

reported for rats treated with 54% chlorine PCBs (NCI, 1978), but these occurred at very low incidences which were not statistically significant. Moreover, it is uncertain whether any of the rat tumors observed after chronic feeding of 54% chlorine PCBs were truly malignant. The more detailed data available for PCB mixtures of 60% chlorine content clearly indicate that while the tumors are pathologically classified as hepatocellular carcinoma, they do not metastasize nor do they shorten life span (Kimbrough et al., 1975; Schaeffer et al., 1984; Norback and Weltman, 1985; Young, 1985). While uncertainties as to the process of chemical carcinogenesis may justify making certain conservative assumptions when deriving quantitative estimates from the animal data for regulatory purposes, this does not justify the portrayal of the qualitative cancer hazard in humans as high when the tumors apparently have little in common with the malignant tumors classified as cancer in humans.

3.2.2.5 Recurrent Liver Injury and Nongenotoxic Carcinogens

The last issue relevant to an evaluation of the possible human risk from exposure to PCB mixtures containing 54% chlorine is that they are nongenotoxic agents which cause mouse liver tumors only at hepatotoxic doses (see Figure 2). Nongenotoxic agents may be cancer promoters, yet the initiation of cancer depends upon the actions of other agents (e.g., endogenous hormones or unrelated carcinogens in the diet) or processes (e.g., genetic defects of inbred animal strains). The promoting ability of nongenotoxic agents like 54% chlorine PCB mixtures clearly depends upon a chronic dose threshold at or above which recurrent liver injury is consistently observed. For example, Nagasaki et al. (1972) and Kimbrough and Linder (1974) observed liver tumors and hepatic necrosis in mice at dietary dose levels of 500 ppm and 300 ppm, respectively; yet lower doses of 54% chlorine PCB mixtures caused no liver tumors and changes in liver histopathology suggestive of hepatotoxicity were dramatically reduced. While the 500 ppm diet induced a 53% incidence of hyperplastic nodules and a 41% incidence of hepatocellular carcinoma in male mice, *no hyperplastic nodules or carcinomas* were observed at doses of 250 ppm or lower.

It has been argued that hepatotoxicity may nonspecifically promote the selection and growth of spontaneous liver tumors whose incidence is commonly high in mice (Marks, 1976; Schulte-Herman et al., 1983; Flavin, 1984). The elevated spontaneous liver tumor incidence in mice is also of concern because the tumor rate appears to depend upon factors independent of the test chemical, e.g.,

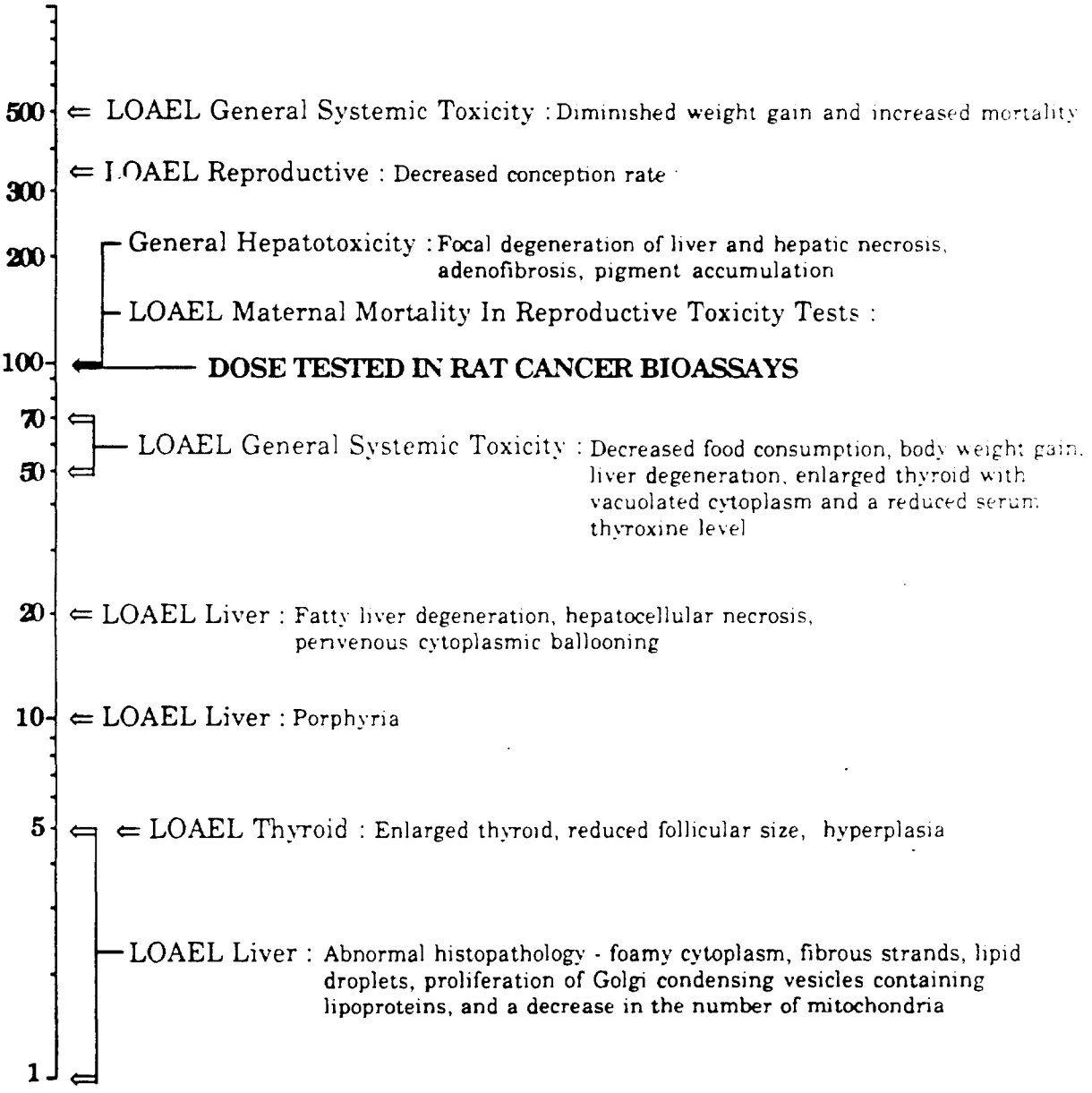


Figure 2

Dose-Response Relationships in the Rat By Dietary Levels (ppm) of 54% Chlorine PCB Mixtures

sex and strain differences, conditions leading to certain physiological changes, or dietary influences. The Nutrition Foundation (1983) has suggested:

> *Less concern is warranted in the case of chemical induction of tumors only in mouse liver, particularly if the tumors are primarily benign neoplasms, that are associated with only the high exposure levels that produce additional biological effects such as chronic tissue injury. Further evidence that would alleviate concern would include evidence that the substance fails to bind covalently to cellular macromolecules and negative results in short-term in vivo and in vitro tests for DNA damage. In such an instance there would be little basis for severely restricting exposure to a chemical.*

PCB mixtures of 54% chlorine content have these same characteristics. They are not genotoxic; they are carcinogenic in the mouse liver but only at clearly hepatotoxic doses, but not carcinogenic in the rat. Therefore, the weight of evidence for these mixtures suggests the animal data have limited human relevance.

Ward et al. (1989) recently compared the hepatotoxicity of chemicals which induce putative preneoplastic liver foci (GST-P positive foci) with chemicals which do not induce these foci. In a discussion of their findings, these investigators concluded that their results:

> *... clearly showed that agents which enhanced the formation of GST-P positive foci (promoters) were generally hepatotoxic at doses which were also promoting, while nonpromoters were not hepatotoxic."* These authors further stated: "*The majority of tumor promoters are generally toxic to the target organ in which the promoter exerts its tumor-promoting activity (J. Ward, unpublished observations). Obviously, the biologic activity of tumor promotion is, in and of itself, a biologic phenomenon which can be characterized as organ-specific toxicity (Schulte-Herman, 1983). When a chemical exerts no organ-specific toxicity, as measured by histopathological lesions or biochemical parameters, it would have a low probability of possessing tumor-promoting activity. ... If the tumor-promoting activity of a chemical was dependent, as expected, on dose and liver toxicity, one would not expect the chemical to be a promoter at doses below which some degree of hepatotoxicity or hepatocyte adaptation would be seen.*
> **(emphasis added).**

These findings have important implications for an evaluation of the issue of human carcinogenicity of 54% chlorine PCB mixtures. As stated by Ward,

promoter chemicals would not be expected to promote tumor development at doses below those necessary to cause hepatotoxic changes. The 54% chlorine PCB mixtures mirror this general characteristic of promoters in that tumors do not develop in mice at doses which either are not hepatotoxic or are at least distinctly less toxic.

The relationship between recurrent liver injury and hepatic tumor development in studies of 54% chlorine PCB mixtures in rats is also important. Chronic bioassays have been performed in rats at dietary levels of 100 ppm and 1,000 ppm, doses which are clearly hepatotoxic (see Figure 2), and the review of the NCI bioassay results performed by the Clearinghouse on Environmental Carcinogens concluded Aroclor 1254 may be acting as a promoter at a dose of 100 ppm. Disseminated single-cell or focal coagulative necrosis (Baumann et al., 1983), enlarged hepatocytes, cytoplasmic inclusions, foamy cytoplasm (Kimbrough et al., 1974), and moderate fatty liver degeneration (Chu et al., 1977) have all been reported for 54% chlorine PCB mixtures at dietary doses as low as 20 ppm. The hepatotoxicity of Aroclor 1254 is increased at doses of 100 ppm and at this dose hepatic injury was a major cause of lethality in the NCI bioassay (Ward, 1985). Also, as with the mouse, lower doses of 54% chlorine PCB mixtures (Aroclor 1254) were not associated with significant increases in liver tumors. Thus, it is noted that the sex and species dependency of the tumorigenicity of 54% chlorine PCB mixtures corresponds to clear sex and species related differences in both hepatotoxicity and also the incidence of spontaneous liver tumors. When taken together with the negative genotoxicity studies, these findings suggest 54% chlorine PCB mixtures are only promoting the growth of spontaneously-arising liver tumors in mice by inducing liver injury. The belief that recurrent tissue injury acts as a nonspecific promoter of tumors in the affected tissue has been reviewed by others (Stott et al., 1981; ECETOC, 1982; Flavin, 1984), and some of the mechanisms whereby tumors are promoted or induced secondary to recurrent tissue injury are listed below:

1. Cytotoxicity increases cell replication and, therefore, DNA synthesis, causing an increase in the spontaneous mutation rate.

2. Cytotoxicity shortens the cell cycle during which tissue is regenerated, thus leaving less time for DNA repair mechanisms to eliminate misincorporated bases or alkylated bases.

3. Cytotoxicity alters the levels of critical nucleotide pools, ions, and enzymes.

4. The increase in DNA synthesis in regenerating tissue means more genes are in the transcribable state and are more susceptible to the loss of regulatory control by a mutation in a regulatory gene locus.

5. Cytotoxicity may alter cellular methylase or polymerase activity.

6. Cytotoxicity is a stimulus for cellular proliferation which could result in hyperplasia. It may selectively remove cells that are less proliferative allowing previously initiated cells to grow.

7. Cytotoxicity and inflammation may enhance the formation of superoxides, hydrogen peroxides, hydroxy radicals and other peroxide products that may endogenously mutate DNA.

Given the numerous mechanisms whereby recurrent tissue injury results in tumor formation, and the number of nongenotoxic and/or relatively nontoxic chemicals for which this mechanism might apply (ECETOC, 1982), it is not surprising that many scientists view high-dose hepatocarcinogenesis in a species with a high spontaneous tumor incidence like the mouse with some skepticism. In fact, this problem has caused some scientists to voice concern that a high percentage of all chemicals, man-made and natural, will ultimately be shown to cause tumors in animals (especially if tested in species with high background tumor incidences at maximally tolerated doses), thereby becoming classified as carcinogens. This potential confounder represents a major interpretative problem when considering the limited animal data available for 54% PCBs.

3.2.3 Qualitative Assessment of the Carcinogenicity of 60% PCB Mixtures

In rats, a dose of 100 ppm of 60% chlorine PCBs appears to represent the maximally tolerated dose, and three studies have reported hepatocellular carcinomas in rats using a dosing regimen of approximately 100 ppm. A review of these three studies indicates that the tumors occurred very late in the life of the animal, with a significant incidence of tumors only beginning to appear after about two years of exposure. Of interest is the fact that PCB treatment, while increasing the incidence of liver cancer, did not increase the total tumor incidence of treated animals. The total tumor incidence was not increased in these studies because the incidence of other tumor types had been significantly decreased. This suggestion of antitumor activity of PCBs has also been demonstrated in a study examining the effect of PCB exposure on the final tumor incidence in animals following the transplantation of the Walker 256 sarcoma.

The effects of chronic PCB treatment were not life shortening, and in fact in two of the studies the morbidity and mortality of the animals were actually decreased by PCB treatment. While the tumors are described as malignant in these studies, i.e. hepatocellular carcinomas, in none of the studies did the liver tumors metastasize to other organs even though metastases would be expected if the tumors were truly malignant. Thus, the qualitative human relevance of the carcinogenic potential of 60% PCBs based on the animal data is limited. There are other considerations which lessen concern over the carcinogenic data of 60% PCBs. PCBs as a class of compounds are not mutagenic; therefore tumorigenesis for these compounds would appear to involve an epigenetic, threshold-dependent mechanism. There is also substantial evidence that the doses used to induce tumors in rats were hepatotoxic, and evidence suggesting the neoplasms induced by different PCB mixtures are reversible if the exposure is terminated before the animal has been exposed for a considerable portion of the animal's lifespan. All of these findings seriously undermine the human relevance of the animal carcinogenicity data. This is particularly true as the human dosages from past and present human exposures are far lower than those used in the animal studies. Therefore, while it is concluded there is sufficient animal evidence that PCBs of 60% chlorine content (e.g., Aroclor 1260/Clophen A60) are carcinogenic in rats, several features of these studies limit the human relevance of this finding.

3.3 Classification of the Carcinogenic Potential of the PCB Mixtures

When classifying chemicals as carcinogenic agents, the evaluation must consider both human and animal evidence. Where there is limited or insufficient evidence of human carcinogenicity, the evaluation rests primarily with the animal data and a determination of its human relevance. The following sections of this document list the IARC and USEPA criteria and recommended methodologies for weighing the human and animal evidence of a chemical's carcinogenic potential. These criteria are then separately applied to the PCB data reviewed in section 2.0 to arrive at the predicted classification of various PCB mixtures using these IARC or USEPA classification criteria.

3.3.1 The IARC Carcinogen Classification Criteria

The IARC classifies the carcinogenic potential of chemicals based on the following considerations:

"Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of the carcinogenicity of an agent. In considering all of the relevant data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

(a) Degrees of evidence for carcinogenicity to humans and to experimental animals and supporting evidence.

It should be noted that these categories refer only to the strength of the evidence that these agents are carcinogenic and not to the extent of their carcinogenic activity (potency) nor to the mechanism involved. The classification of some agents may change as new information becomes available.

(i) Human carcinogenicity data

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between exposure to the agent and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of doses to which human beings are known to be exposed, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. A conclusion of 'evidence suggesting lack of carcinogenicity' is inevitably limited to the cancer sites, circumstances and doses of exposure and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studies can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence for the carcinogenicity of the agent for specific organs or tissues.

(ii) Experimental carcinogenicity data

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms (as described on P.23) in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

Exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset

In the absence of adequate data on humans, it is biologically plausible and prudent to regard agents for which there is *sufficient evidence* of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g., (a) the evidence of carcinogenicity is restricted to a single experiment; or (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study; or (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of evidence suggesting lack of carcinogenicity is inevitably limited to the species, tumour sites and doses of exposure studied.

(iii) Supporting evidence of carcinogenicity

The other relevant data judged to be of sufficient importance as to affect the making of the overall evaluation are indicated.

(b) Overall evaluation

Finally, the total body of evidence is taken into account; the agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement, reflecting the strength of the evidence derived from studies in humans and in experimental animals and from other relevant data.

Group 1 -- The agent is carcinogenic to humans.

This category is used only when there is *sufficient evidence* of carcinogenicity in humans.

Group 2

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as agents for which, at the other extreme, there are no human data but for which there is experimental evidence of carcinogenicity. Agents are assigned to either 2A (probably carcinogenic) or 2B (possibly carcinogenic) on the basis of epidemiological, experimental and other relevant data.

Group 2A -- The agent is probably carcinogenic to humans.

This category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. Exceptionally, an agent may be classified into this category solely on the basis of limited evidence of carcinogenicity in humans or of sufficient evidence of carcinogenicity in experimental animals strengthened by supporting evidence from other relevant data.

Group 2B -- The agent is possibly carcinogenic to humans.

This category is generally used for agents for which there is limited evidence in humans in the absence of sufficient evidence in experimental animals. It may also be used when there is inadequate evidence of carcinogenicity in experimental animals. In some instances, an agent for which there is inadequate evidence or no data in humans but limited evidence of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

Group 3 -- The agent is not classifiable as to its carcinogenicity to humans.

Agents are placed in this category when they do not fall into any other group.

Group 4 -- The agent is probably not carcinogenic to humans.

This category is used for agents for which there is evidence suggesting lack of carcinogenicity in humans together with evidence suggesting lack of carcinogenicity in experimental animals. In some circumstances, agents for which there is inadequate evidence of or no data on carcinogenicity in humans but evidence suggesting lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group."

3.3.1.1 Accurate IARC Classification of Individual PCB Mixtures

Several studies have examined the causes of mortality among workers occupationally exposed to PCBs. When the mortality studies are considered collectively, most of the epidemiological evidence for human carcinogenicity is negative. While some associations have tentatively been suggested, no study attempted to control or correct for confounders and this obvious shortcoming prevents any of the suggested associations from being considered causal (Bertazzi

et al., 1987; Brown, 1987). Until larger epidemiological studies can be completed, that is, until a larger number of the persons included in these cohort studies have died, the collective PCB epidemiology data must be considered to provide *inadequate evidence of carcinogenicity*. Therefore, the animal evidence of carcinogenicity for each PCB mixture becomes the deciding factor for the final classification of each mixture.

The animal data have been carefully reviewed. It is quite clear from the available animal cancer literature concerning 42% chlorine PCB mixtures that these mixtures do not exert a carcinogenic response when chronically administered to rats or mice. While Schaeffer et al. (1984) did note an increased incidence of neoplastic nodules, the biological relevance of this finding is severely limited by the fact that these neoplasms had not progressed to benign or malignant tumors after a lifetime of exposure (i.e., the lesions appear to have no carcinogenic potential). These data would categorize the animal evidence as *inadequate evidence of carcinogenicity*. Because the other rodent bioassays were of less than a lifetime duration, the 42% animal data fall just short of the criteria necessary for establishing *evidence suggesting a lack of carcinogenicity*. Given the human and animal data, 42% chlorine PCBs should be classified as Group 3, possibly Group 4, chemicals. Group 3 represents those chemicals "*not classifiable as to its carcinogenicty.*" Alternatively they might be considered Group 4 since: "*In some circumstances, agents for which there is inadequate evidence of or no data on carcinogenicity in humans but evidence suggesting lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.*" Since 42% PCBs are not genotoxic, and have yielded negative results in three studies testing two species, the Group 4 classification is clearly a potential classification.

The animal carcinogenicity studies of 54% chlorine PCB mixtures are more difficult to interpret. While an increased incidence in mouse liver tumors has been reported in two different studies, several features of this response limit its relevance. These features are, 1) the tumorigenic response was limited to male mice; and 2) the tumorigenic response was not seen at slightly lower doses causing less severe liver effects. The rat studies employed either a limited number of animals or a less than lifetime exposure duration; overall the rat data were negative. In our review of the mouse data we have also noted the general scientific concern for positive mouse liver tumor data, especially when, 1) the data

are sex and dose specific, 2) it occurs at doses inducing a condition of chronic tissue injury, and 3) it is not supported by positive findings in other species. After considering all of this evidence, we conclude there is *limited evidence of carcinogenicity* for PCB mixtures of 54% chlorine content (i.e., *(c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains.* (emphasis added). Given this and the inadequate human evidence it is concluded that 54% chlorine PCBs should be classified as Group 3 chemicals. The supporting evidence that might be considered as the basis for altering this classification, i.e., lack of mutagenic potential and conditions of chronic toxicity in the target organ, tend to strengthen the Group 3 classification rather than suggest a possible 2B consideration. In support of this position we note that several chemicals (Table 3.4), including those which are persistent, hepatotoxic chlorinated hydrocarbons like PCBs, and those which have produced liver tumors in mice but provide negative or inconclusive evidence in rats, have been listed by IARC as Group 3 carcinogens (IARC, 1987). These chemicals include aldrin, chlordane, chrysoidine, diazepam, dieldrin, and heptachlor. Group 3 distinctions are not limited to situations in which the only positive data are mouse liver tumor data. Cyclamates are also Group 3 chemicals. This classification was reached after noting that although cyclamates do increase bladder tumors and lymphosarcomas in mice, they produce largely negative responses in the rat. Similarly, isoniazid, a Group 3 chemical, produces lung tumors in the mouse but is negative in the hamster. Thus, listing 54% chlorine PCBs as a Group 3 carcinogen would be consistent with IARC's guidelines and the clear precedence IARC has established for other chemicals with similarly limited or insufficient animal data.

Concerning the animal carcinogenicity of 60% PCB mixtures, hepatocellular carcinoma has been reported in three separate studies providing *sufficient evidence of carcinogenicity*. There are, however, a number of consistent features of these data indicating the animal carcinogenicity of 60% PCBs is of limited biological relevance to humans. To summarize, these features are: 1) The tumors occur very late in the life of the animal at apparently MTD doses; 2) 60% PCBs never increased the total tumor load, and while increasing the incidence of liver tumors, they also decreased the incidence of other neoplasms (other studies also suggest antitumor activity with specific tumors); 3) The tumors did not behave like malignant tumors, i.e., no metastases were reported even though an approximate 50-90 hepatocellular carcinoma incidence was reported in two

Table 3.4

Comparative Animal/Human Evidence of Carcinogenicity for Some of the Compounds Listed as Group 3 Chemicals

Chemical	Bioassay Result		Human Evidence	IARC Class
	Rat	Mouse		
Aldrin	Negative or equivocal	Liver neoplasms	Inadequate	Group 3
Dieldrin	Negative	Liver neoplasms	Inadequate	Group 3
Chlordane	Inconclusive	Liver neoplasms	Inadequate	Group 3
Chrysoidine	Inadequate	Liver adenomas & carcinomas, leukemia	Inadequate	Group 3
Diazepam	Negative	Liver tumors	Inadequate	Group 3
Heptachlor	Inconclusive	Liver neoplasms	Inadequate	Group 3
Isoniazid	Inadequate	Lung tumors	Inadequate	Group 3
Cyclamates	Bladder tumors	Lymphosarcomas	Inadequate	Group 3
N-phenyl-2-naphthylamine	Negative	Liver neoplasms & other neoplasms	Inadequate	Group 3
5-Azacytidine	Negative	Malignant neoplasms	ND	Group 3
Bis-(2-chloro-1-methyl)ether	Negative	Malignant & benign neoplasms	ND	Group 3
2,6-Dichloro-p-phenylene diamine	Negative	Malignant & benign neoplasms	ND	Group 3
Di(2-ethylhexyl)-adipate	Negative	Malignant & benign neoplasms	ND	Group 3
Pentachloroethane	Negative	Malignant & benign neoplasms	ND	Group 3
1,1,1,2-Tetrachloroethane	Negative	Malignant & benign neoplasms	ND	Group 3
1,1,1-Trichloroethane	Negative	Malignant neoplasms	ND	Group 3
Trichloroethylene	Negative	Malignant & benign neoplasms	Inadequate	Group 3
Zearalenone	Negative	Benign neoplasms	ND	Group 3

ND = no adequate data
Adapted from: Tennant et al., (1986) and IARC (1987)

studies; and 4) The tumors were not life-shortening; on the contrary PCB-treated animals tended to live significantly longer than the untreated animals. Given the limited biological relevance of these tumors, the lack of mutagenic potential, and the fact that chronic systemic and liver toxicity occurs at the doses tested, it is concluded that the classification of 60% PCB mixtures should be no higher than 2B.

3.3.1.2 Limitations of the Current IARC Classification of PCBs

After reviewing the animal and human data on PCBs as a class of compounds, we conclude that the working group responsible for current IARC classification of PCBs has made two serious errors. First, the working group failed to acknowledge the differences in toxic potency or toxic effects among the various PCB mixtures and did not attempt to classify each mixture according to the animal data specific for each mixture. Second, the working group misclassified the weight of evidence provided by the epidemiology studies.

The current IARC classification for human data on PCBs is *limited evidence of carcinogenicity* (IARC, 1987). This finding relied heavily on the reports of Yusho and Yu-Cheng poisonings as well as the reports of Bertazzi and coworkers (1981 and 1987). The current consensus of scientific opinion is that the human effects resulting from exposure to contaminated rice oil in Japan and Taiwan are better correlated with exposure to polychlorinated dibenzofurans [see the Toxicant Profile for a more detailed review of this issue, (TERRA,1988)]. Analysis of studies emanating from these unfortunate incidents should not be applicable to decisions on the carcinogenic potential for PCBs. The studies of Bertazzi et al. (1981, 1987) are found to contain five serious flaws which severely limit their usefulness in determining carcinogenic potential for PCBs: 1) Use of combined cancer categories to gain statistical significance for their observations; 2) Lack of association between any cause of mortality and duration of exposure, latency, or first year of exposure; 3) Enlarging the cohort with persons only minimally exposed to PCBs did not alter an observation of excess cancer, suggesting PCBs were not the causative agents; 4) Apparent associations between exposure and cancer are sex-specific; and 5) Potential confounders in cohort mortality were not identified and controlled. In fact, Bertazzi et al. conclude that their failure to

exclude confounders precludes a causal association from being reached. Furthermore, as summarized in section 2 of this document and in more detail elsewhere (TERRA, 1988), the epidemiology studies are of *insufficient quality, consistency or statistical power to permit a conclusion regarding causal association*, characteristics of the data that limit it to a classification of *inadequate evidence* according to the IARC classification scheme. Since similar conclusions were reached by the authors of the individual studies (Bertazzi et al., 1987; Brown, 1987), and as the working group did not consider the negative studies of Zack and Musch (1979) and Nicholson et al. (1987), we fail to see how the Working Group could consider the human evidence *limited* rather than *inadequate*.

3.3.2 The USEPA Carcinogen Classification Criteria

The USEPA classification system is an adaptation of the IARC classification scheme (USEPA, 1986) with the following modifications: 1) A "no data" classification has been added; 2) A "no evidence of carcinogenicity" classification has been added; and 3) Consideration of life-threatening benign tumors has been included. For the purposes of discussing the qualitative assessment of PCB mixtures, the USEPA's weight of evidence guidelines for human and animal carcinogenicity studies are quoted below.

"The weight of evidence for carcinogenicity from studies in humans is classified as follows:

1. Sufficient evidence of carcinogenicity, which indicates that there is a causal relationship between the agent and human cancer.
2. Limited evidence of carcinogenicity, which indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding could not be adequately excluded.
3. Inadequate evidence, which indicates that one of two conditions prevailed: (a) there were few pertinent data, or (b) the available studies, while showing evidence of association, did not exclude chance, bias, or confounding and therefore a causal interpretation is not credible.
4. No data, which indicates that data are not available.
5. No evidence, which indicates that no association was found between the exposure and an increased risk of cancer in well-designed and well-conducted independent analytical epidemiological studies.

Assessments for the weight of evidence for carcinogenicity for studies in experimental animals are classified in the following five groups:

1. Sufficient evidence of carcinogenicity, which indicates that there is an increased incidence of malignant tumors or combined malignant and benign tumors; (a) in multiple species or strains; or (b) in multiple experiments (e.g., with different routes of administration or using different dose levels); or (c) to an unusual degree in a single experiment with regard to high incidence, unusual site or type of tumor, or early age at onset.

2. Limited evidence of carcinogenicity, which means that the data suggest a carcinogenic effect but are limited because: (a) studies involve a single species, strain, or experiment and do not meet the criteria for sufficient evidence [see section IV.B.1.c]; (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) an increase in the incidence of benign tumors only.

3. Inadequate evidence, which indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect.

4. No data, which indicates that data are not available.

5. No evidence, which indicates that there is no increased incidence of neoplasms in at least two well-designed and well-conducted studies in different species.

The classifications 'sufficient evidence' and 'limited evidence' refer only to the weight of the experimental evidence that these agents are carcinogenic and not to the potency of their carcinogenic action."

3.3.2.1 Accurate USEPA Classification of Individual PCB Mixtures

As previously stated, the epidemiologic evidence for carcinogenicity resulting from exposure to PCBs is not compelling. In no case are the data strong enough to allow causal inference. Several epidemiology studies have reported no association between PCB exposure and cancer. In both the Bertazzi and Brown studies the authors themselves recognize serious shortcomings in their data. Any correlation between dose or reasonable latency period and cancer incidence was absent in both studies. Also, potential confounders were not controlled for or excluded in any of the studies reported to date. Since causal inference cannot be made due to this failure to exclude confounding variables, and given the conflicting results reported, it is concluded that the weight of evidence for carcinogenicty of PCBs in humans should lead to a classification of *inadequate evidence*. As with the IARC process the animal evidence for carcinogenicity then becomes the deciding factor in the final classification of each PCB mixture.

Reported data from animal studies with 42% chlorine PCB mixtures have not indicated a potential to induce cancer in experimental rodents. For the one study that was conducted over the lifetime of the animal (Schaeffer et al., 1984), no statistically significant increase in carcinomas was observed in rat liver. Exposure to higher doses over shorter periods of time in mice and rats (Ito et al., 1973a&b; Ito et al., 1974) did not give evidence for induction of carcinomas. In fact not even pre-neoplastic lesions were observed in mice exposed to Kanechlor 300 for 32 weeks. Since there is but a single negative lifetime study at a single dose and in a single species, the data for animal carcinogenicity of 42% chlorine mixtures should be judged as providing either *inadequate* or *no evidence* of carcinogenicity. Given these classifications of the animal and human data, 42% PCB mixtures should be classified as group D chemical carcinogens: "not classifiable as to human carcinogenicity."

Two experiments conducted in mice, both for less than lifetime, provide suggestive evidence that exposure to very high doses of 54% chlorine mixtures produces benign or malignant lesions (Kimbrough and Linder, 1974; Ito et al., 1973a&b). While an increased incidence in mouse liver tumors has been reported in two different studies, several features of this response limit its relevance. The tumorigenic response was limited to male mice; it was not seen at slightly lower doses causing causing some derangement of liver pathology, and this response was not supported by the rat data. It is concluded that the data for animal carcinogenicity from exposure to 54% chlorine mixtures should be classified as no more positive than *limited evidence* owing to conflicting interpretations of the one lifetime bioassay and because the mouse studies suffer from 'inadequate duration of exposure,' 'inadequate period of follow-up,' 'too few animals,' and 'inadequate reporting,' all experimental design features which relegate a study to one of *limited evidence*. This along with the *inadequate evidence* from human data, argues for classification of 54% chlorine PCB mixtures as Group C carcinogens.

Clearly bioassays with 60% chlorine PCB mixtures indicate a carcinogenic potential for the class (Kimbrough et al., 1975; Schaeffer et al., 1984; Norback and Weltman, 1985). Three studies have been conducted, all for significant portions of the lifespan of the rats; and all produced significant increases in hepatocellular

carcinomas in either male or female animals. No other species has been tested, so species variability cannot be assessed. Also, data from the studies conducted with the lesser chlorinated PCB classes indicate a trend with increasing chlorination producing increased progression of liver cancer tumor types. Yet the limitations of these data with regard to its biological relevance to humans warrant questioning. Thus, for 60% chlorine PCB mixtures there appears to be *sufficient* evidence for carcinogenicity in animals but *inadequate* human evidence, a combination which normally leads to a Group B2 classification.

3.3.2.2 Limitations of the Current USEPA Classification of PCBs

The USEPA, while recognizing the differences in toxicity or potency of commercial PCB mixtures, fails to recognize these differences when classifying the carcinogenic potential of PCBs and has categorized them collectively as B2. While we agree that this classification would fit the data for 60% mixtures, it should not be attached to mixtures of 42% or 54% chlorine content. The major problem with the simplistic approach to characterizing PCB carcinogenicity used by the USEPA is that it can create unnecessary, inappropriate characterizations of the potential hazards involved with PCB exposure. This problem is similar to one that exists for the polycyclic aromatic hydrocarbons, which the USEPA often treats as a single toxicologic entity even though there are vast differences in toxicity among the different members of this class. As a consequence of this approach, at Superfund sites the risks may be driven by environmental concentrations of relatively innocuous, noncarcinogenic members like pyrene or phenanthrene, for the USEPA treats the entire polycyclic aromatic hydrocarbon class as a single compound and assumes a cancer potency estimate derived for one of its most toxic members, benzo(a)pyrene. Interestingly, while toxicologic differences among PCB mixtures have been largely ignored by the USEPA in its regulatory approach to PCBs, the USEPA has adopted an approach to dealing with polychlorinated dibenzodioxins (PCDDs) that recognizes congener differences in toxicity, and assigns differences in toxic potency to various PCDDs. This difference in the manner in which the health hazards of PCBs and PCDDs are evaluated cannot be justified based upon more extensive data for PCDDs -- it simply does not exist. Thus, in spite of the fact that the assigned differences in congener potency for PCDDs are based on a modicum of data, the USEPA has

utilized this approach since it is at least logical. Although as with PCDDs there is at present insufficient data to support truly congener-based toxicologic evaluations for PCBs, at least the PCB mixtures in question have undergone extensive toxicological testing (information all PCDD mixtures lack). Thus, our recommendation is similar to that of the USEPA's Halogenated Organics Subcommittee (of the Scientific Advisory Board). That is, it is currently more appropriate to evaluate each mixture on the basis of the data available for that mixture, or a mixture closely resembling it, rather than treating all PCB mixtures as though they were a single entity.

3.3.3 Summary and Conclusions

In summary, an objective evaluation of the separate bodies of evidence concerning the carcinogenicity of PCB mixtures reveals distinctly different neoplastic responses. This and the well established differences in PCB mixtures for potency or toxicity indicate each mixture should be classified separately to recognize the distinct differences which exist among PCB mixtures. Using both the IARC and USEPA classification schemes, it is believed the following classifications of the human and animal data should be utilized.

- Most of the epidemiological evidence for human carcinogenicity of PCBs is negative, or at best, weak. As such, until larger epidemiological studies can be completed, the data must be considered *inadequate* to characterize PCBs as human carcinogens.

- PCB mixtures of 42% chlorine content have been tested for carcinogenicity in rats and mice and have shown no significant carcinogenic response after chronic, high dose administration. As such, there is *inadequate / no evidence* of carcinogenicity for 42% chlorine PCB mixtures in animals.

- PCB mixtures of 54% chlorine content have demonstrated carcinogenic potential only in the mouse liver; the rat data are considered less than ideal but negative. Given the serious experimental design problems inherent to the mouse studies, and the limited biological relevance of mouse liver tumor data in general, the animal carcinogenicity data for 54% PCB mixtures should be considered to be *limited*.

- Positive animal carcinogenicity results obtained for 60% chlorine PCB mixtures demonstrate the nonmalignant behavior of PCB-induced tumors and the lack of expected trends: no increase in total site-specific cancers; no shortening of the lifespan due to cancer; no metastases found; and no early-

life tumors in rats. Thus, while the animal evidence is considered *sufficient*, concern is lessened by the apparently limited relevance of the reported findings to the human condition of cancer.

- Two features of PCB toxicology moderate concern for the preceding findings. PCBs have no apparent genotoxic or mutagenic potential and do not bind to nucleic acids, as demonstrated in numerous studies both *in vitro* and *in vivo*. PCBs cause liver hypertrophy and hepatotoxicity at the doses tested for carcinogenicity; thus promotional pressure secondary to known physiologic changes or systemic toxicity is a relevant consideration.

Based on these characterizations, and by analogy to chemicals or mixtures which have undergone similar data review and critique by USEPA and IARC, we conclude that the following data classifications for the potential carcinogenicity of 42% and 54% chlorine PCB mixtures are objective and justifiable.

<u>42% Chlorine PCB Mixture Classifications:</u>

- **USEPA**: Group D
- **IARC**: Group 3/Group 4

<u>54% Chlorine PCB Mixture Classifications:</u>

- **USEPA**: Group C
- **IARC**: Group 3

<u>60% Chlorine PCB Mixture Classifications:</u>

- **USEPA**: Group B2
- **IARC**: Group 2B

As has been shown above, not all PCB mixtures need be relegated to the same classification category by either of the agencies which classify chemicals tested for carcinogenicity. There is a clear distinction among the three PCB mixtures evaluated which would allow regulation of these mixtures under different sets of assumptions. PCB mixtures which are 42% chlorine are clearly not carcinogenic. On the basis of long-term bioassays conducted in rats, 60% chlorine PCB mixtures have been repeatedly shown to possess carcinogenic potential even though occupational exposure to PCBs has not resulted in the induction of excess cancers. Occupying the middle regulatory ground are the 54% chlorine PCB mixtures where both the animal and human carcinogenicity data are insufficient

to reliably predict potential for the induction of cancer in man. There is some latitude, then, for determining how to establish Acceptable Daily Intakes (ADIs) which for the purposes of this document are equivalent to EPA's Risk Reference Dose, for 54% chlorine PCB mixtures.

4.0 QUANTITATIVE ASSESSMENT OF PCB MIXTURES

Different approaches are employed in deriving quantitative evaluations of toxicity depending on whether or not the chemical is a potential carcinogen. For compounds with the potential to cause cancer in humans, the probability of inducing cancer is associated with a particular dose or exposure. Often, a dose or exposure level is sought that carries a cancer risk considered acceptably low (typically a probability of 1:10,000 to 1:1,000,000). For noncarcinogenic compounds, safe human exposure levels are developed using the safety factor or threshold approach. The final number representing the safe human dosage, typically referred to as an "Allowable Daily Intake" (ADI), is derived by applying certain safety factors to the NOAEL or LOAEL identified in the qualitative assessment. The criteria used for selection of safety factors are provided in Table 4.1.

Table 4.1
Safety Factors for Extrapolation of Animal Data to Man

Safety Factor	Guideline for Use
1-10	A safety factor of 1-10 is used when the extrapolation is made from sufficient human data. This safety factor is used to correct for possible sensitive populations, i.e., intraspecies variations. (Total safety factor is ≤10).
1-10	An additional safety factor of 1-10 is added when the extrapolation is made from adequate chronic animal studies. This safely corrects for possible interspecies variations. (Total safety factor becomes ≤100)
1-10	An additional safety factor of 1-10 is added when the extrapolation is made from more limited animal data. For example, when the availability of chronic data or number of species tested is considered to be inadequate or when subchronic data are used. (Total safety factor becomes ≤1,000)
1-10	Additional safety factor of 1-10 is used when extrapolating from the LOAEL rather than a NOAEL. (Total safety factor becomes ≤10,000)

In section 3.0 of this report it was concluded that 42% chlorine PCB mixtures should be classified either as Group-D chemicals (according to the USEPA classification scheme) or Group-3/Group-4 chemicals (according to IARC classification guidelines). This indicates that a carcinogenic potential cannot be deduced from the data set currently available. Therefore, it is inappropriate to use nonthreshold extrapolation procedures in the quantitative assessment for these mixtures.

In section 3.0 of this report it was concluded that 54% chlorine PCB mixtures should be classified as Group-C chemicals (according to the USEPA classification scheme) or Group-3 chemicals (according to IARC classification guidelines). This reflects the lack of carcinogenic potential in rats and the fact that as an epigenetic carcinogen in mice the observed carcinogenic effects should have a threshold. Therefore, it is inappropriate to use nonthreshold extrapolation procedures in the quantitative assessment for these mixtures.

In the next section, ADI values are developed for 42% and 54% chlorine PCB mixtures. Studies in animals have clearly indicated tumorigenic potential for 60% chlorine PCB mixtures, and safe human exposure guidelines for these mixtures are consequently based upon a cancer risk extrapolation from rodent bioassay data and are provided in section 4.2.

4.1 Development of Allowable Daily Intake Values for 42% and 54% Chlorine PCB Mixtures

There have been a number of studies of human populations exposed to significant levels of 42% and 54% chlorine PCBs, permitting ADIs to be calculated from clinical studies. The derivation of an ADI from an adequate human database is always preferable to an ADI derived from animal studies in that it avoids the inherent uncertainties associated with animal-to-human extrapolations. The preferable derivation from human exposure data will be utilized here. As described in section 2.3, the typical PCB dosage received by a capacitor worker was about 50-60 μg/kg/day, and the PCB mixtures to which they were exposed were primarily 41% to 54% in average chlorine content. Our review of the many health effects studies of capacitor workers, as well as recent reviews by others (Kimbrough, 1987; 1988), indicate that these dosages were associated

with no discernable adverse health effects and therefore represent a reasonable NOAEL for 42% and 54% chlorine PCBs in humans. It is possible that these studies did not evaluate "sensitive" humans, since they included only adult worker populations. Therefore, it is appropriate to use a safety factor of 10 in the development of an ADI for protection of potentially sensitive populations (see Table 4.1). When this safety factor is applied, an ADI of **5 μg/kg/day** is calculated.

While the clinical data from which this ADI is derived encompasses exposure to both 42% and 54% chlorine PCBs, precise contribution of one versus the other mixture to total PCB exposure in these populations is often unclear. The NOAEL information derived from animal studies suggests that 54% chlorine PCBs are more potently toxic than 42% chlorine PCBs (see section 2), and it may be inappropriate therefore to use the same ADI for both mixtures. The difference in potency between these two mixtures, based upon NOAELs for the most sensitive organs/tissues in animal studies (see section 3.0), appears to be approximately a factor of two. Because there is some uncertainty in this potency relationship estimation, a factor of five will be selected. Therefore, if a safety factor of 50 [10 for intraspecies variation (i.e., sensitive population) and 5 for greater toxic potency] for 54% chlorine PCBs is applied to the human data, an ADI of **1 μg/kg/day** is derived.

For a 70 kg adult, the adoption of a 5 μg/kg/day ADI for 42% chlorine PCBs would set the upper limit on daily exposure at 350 μg/day, a dose that is 10-12 fold lower than the average dose experienced by capacitor workers as calculated in section 2.3. The allowable workplace exposure at the maximum OSHA workplace air guideline is approximately 28 times greater than this ADI, and potential food exposures as allowed under current USFDA contaminant guidelines also permit higher daily exposures, e.g. from PCBs in fish. **For a 70 kg adult, using a 1 μg/kg/day ADI for 54% chlorine PCBs, the upper limit on daily exposure would be 70 μg/day, a dose that is some 50-60 fold lower than the average dose experienced by capacitor workers, and some 71 times lower than the allowable workplace exposure set by OSHA for 54% chlorine mixtures.**

4.2 Quantitative Assessment of 60% Chlorine PCB Mixtures

In its regulatory policy concerning PCB mixtures, the USEPA has defaulted to the position that all PCB mixtures have a cancer potency which is equal to 60%

chlorine PCB mixtures. However, we believe this position to be scientifically unsupportable in light of the summary of existing animal and human data for 42%, 54%, and 60% chlorine PCB mixtures presented in section 3. Still, in light of its importance to the USEPA's default regulatory policy, we believe it germane to critically evaluate their analysis of carcinogenicity studies of 60% chlorine PCB mixtures and the methods they have used to derive a cancer potency factor.

The data from three bioassays of 60% chlorine PCB mixtures have been included in this analysis (see Table 4.2). Consistently, chronic animal bioassays of different 60% PCB mixtures have demonstrated carcinogenic potential. However, none of the experiments employed more than one dose, and the data from the Norback and Weltman study are flawed because the experiment cannot be interpreted without acknowledging the considerable promotional influence of partial hepatectomy. Unfortunately, by performing partial hepatectomy in a significant portion of the animals tested, the experimental protocol adopted by Norback and Weltman (1985) did not follow NCI guidelines. This problem is further compounded by the fact that this report does not allow one to ascertain the influence of partial hepatectomy on the incidence of malignant tumors observed at the termination of the experiment. For these reasons and those discussed below, all of the cancer potency factors derived from this and other data sets modeled must be viewed with some skepticism since each study suffers some flaw.

Table 4.3 lists cancer potency factor estimates from the studies of Norback and Weltman (1985), Kimbrough et al. (1975), and Schaeffer et al. (1984). Data were modeled using the multistage analysis described by Crump and Crockett (1985). The assumed lifespan for rats was 104 weeks as this represents the duration of exposure and experiment suggested for chronic bioassays (NCI, 1978). None of the above studies was terminated on the 104th week; thus derived factors are presented both with and without correction for experiment length relative to the lifespan of the test animal. To normalize the results of this analysis for differences in length of the experiment, the ratio of experimental length to lifespan has been used. While the data from the various 60% chlorine PCB mixture studies will be modeled both with and without the inclusion of neoplastic nodules, it is our interpretation of the OSTP (1985) guideline that only in cases of rare tumors or mouse liver tumors should data inclusive of neoplastic nodules be summed with malignant and benign tumors. However, the inclusion of neoplastic nodules will be compared here because the USEPA has taken this approach in formulating its cancer potency factor. Currently, USEPA has estimated the cancer potency factor for PCBs to be 7.7 per mg/kg/day, based on

Table 4.2

Summary of PCB Bioassay Data Sets Modeled for 60% Chlorine Mixtures

Species & Sex	Dietary Dosage (ppm)	Number Positive for Liver Lesion		No. Animals Necropsied	Proportion	Reference
		Neoplastic Nodule	Hepato-carcinoma			
Rat, female	0		1	173	1/173	Kimbrough et
	100		26	184	26/184	al., 1975
Rat, female	0	0	1	173	1/173	Kimbrough et
	100	144	26	184	170/184	al., 1975
Rat, male	0		1	131	1/131	Schaeffer et
	100		61	129	61/129	al., 1984
Rat, male	0	5	1	131	6/131	Schaeffer et
	100	63	61	129	124/129	al., 1984
Rat, female	0		0	49	0/49	Norback &
	69		43	47	43/47	Weltman, 1985
Rat, female	0	1	0	49	1/49	Norback &
	69	2	43	47	45/47	Weltman, 1985

results from the Norback and Weltman (1985) study. We have also calculated a similar value using their assumptions (Table 4.3). Like the USEPA, this analysis assumed that progression of neoplastic nodules to carcinomas had been demonstrated by the concurrent histopathological protocol. Also like the USEPA, body surface area was used to predict human equivalent doses. The controversies associated with the use of body surface area dose conversions between species are discussed below.

Table 4.3

Estimated Cancer Potency Factors for 60% Chlorine PCB Mixtures

Reference	Cancer Potency Factor (per mg/kg/day)	
	Surface Area	Body Weight
Corrected for Experiment Length		
Norback & Weltman, 1985	4.8	0.82
Norback & Weltman, 1985[a]	6.5	1.1
Kimbrough et al., 1975	0.25	0.042
Kimbrough et al., 1975[a]	4.0	0.69
Schaeffer, 1984	0.8	0.14
Schaeffer, 1984[a]	4.1	0.71
Not Corrected for Experiment Length		
Norback & Weltman, 1985	5.7	0.98
Norback & Weltman, 1985[a]	7.8	1.3
Kimbrough et al., 1975	0.24	0.04
Kimbrough et al., 1975[a]	3.5	0.61
Schaeffer, 1984	0.91	0.16
Schaeffer, 1984[a]	4.7	0.81

[a] These data include neoplastic nodules, adenomas and carcinomas reported by the authors.

Table 4.4

Summary of Geometric Mean Cancer Potency Factors for 60% Chlorine Mixture Chronic Bioassays

Tumor Data Modeled	Cancer Potency Factor (per mg/kg/day)	
	Surface Area	Body Weight
No adjustment for experiment length		
Tumors	1.07	0.18
Tumors and nodules	5.06	0.87
Adjusted for experiment length		
Tumors	1.04	0.17
Tumors and nodules	4.75	0.81

Geometric means of cancer potency factors derived for 60% chlorine PCB mixtures are shown in Table 4.4. Inclusion of data on neoplastic nodules in the dataset modeled results in an approximate five-fold increase in the derived potency factor compared to data sets where only benign and malignant tumors are considered. If data are adjusted for length of the experiment, a slight smoothing of this difference is produced.

The choice of a scaling method to extrapolate human doses from animal studies is a controversial one. For example, three federal agencies (the Consumer Product Safety Commission, the Food and Drug Administration, and the Environmental Protection Agency) use three different methods to determine human doses from animal experiments. In particular, there is considerable debate as to whether body surface (mg of chemical/m^2 of body surface/day; favored by the EPA) or body weight (mg of chemical/kg body weight/day; favored by the FDA) scaling is more appropriate for determining human doses from animal data. The choice to scale doses by body surface or body weight significantly affects

the cancer potency factor derived from a bioassay. The selection of surface area scaling over body weight essentially increases the cancer potency estimate 6-7 fold if it is based on rat data and some 12-14 fold if the potency estimate is based on mouse data.

The EPA has adopted body surface dose conversions as a matter of policy. Although there is some support for the use of body surface scaling in short term experiments examining noncarcinogenic endpoints, there are no studies which support the use of body surface scaling for extrapolating doses of animal carcinogens to man. In fact, recent evidence lends empirical support to scaling on the basis of body weight for animal carcinogens. In a rigorous analysis of risk assessment methods using data on 44 chemicals which allowed prediction of risk-related doses (RRD) from animal and human data, Crump and co-workers (Allen et al., 1987) determined that if the appropriate analysis method were used, surface area conversion overestimates the RRD by a factor of 8 to 12 while a body weight conversion overestimates by a factor of only 1.1 to 1.7. These data support the use of body weight conversion for determining the human equivalent dose; this change alone in the USEPA data set reduces the cancer potency factor to 1.3 per mg/kg/day.

The studies of Norback and Weltman (1985) and Schaeffer et al. (1984) are unique in that both were conducted over a period of time greater than what is normally considered for a carcinogenicity bioassay. These studies were conducted for periods of 119 and 125 weeks, respectively. According to the data of Schaeffer and coworkers, carcinomas did not appear prior to day 700 (100 weeks) and the majority (61%) of the carcinomas found at necropsy were found in animals sacrificed between days 801 and 832, i. e. weeks 114 to 119. Similarly, data from Norback and Weltman (1985) showed that trabecular carcinomas did not appear until the 15th month and that 2 of the 3 livers examined at the 18 and 24 month time periods had carcinoma; adenocarcinoma was not found in the excised liver sections until the 24th month. Thus, if these experiments had been terminated at the point most carcinogenicity bioassays are, the proportion of animals determined to have neoplastic lesions certainly would have been less. The extension of these bioassays beyond the usual time-frame, and the important contribution of very late-life tumors to the positive results of the studies, make it

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very difficult to interpret the meaning of these studies in comparison with bioassays of other compounds conducted over a conventional 104 week period. In short, the extended experiment duration selected by these investigators enhances the tumor incidence of PCBs, and hence cancer potency estimates, relative to most other carcinogenic chemicals which are tested for 104 weeks as suggested by the National Cancer Institute. Thus, the perceived hazard of PCBs (quantitative assessment) is in a sense falsely magnified relative to most other compounds. It is noted that the State of California has recognized this inconsistency and has suggested correcting for the extended length of the test data.

Where multiple data sets are available for analysis (as is the case with studies on 60% chlorine PCB mixtures), it is most reasonable to calculate a geometric mean of cancer potency factors from appropriate data sets (Allen et al., 1987). Comparing the potency factors for 60% PCB mixtures in rats, the potency factor varies some ten fold among the three studies, and those studies of more than two years in duration have decidedly larger cancer potency estimates. Assuming 1 per 100,000 is an acceptable risk for excess cancers, dose levels causing this level of risk would be 0.0592 μg/kg/day for 60% chlorine PCB mixtures. This risk estimate for 60% chlorine PCB mixtures is based on geometric mean of cancer potency factors determined from body weight conversions of data from the studies of Norback and Weltman (1985), Kimbrough et al., 1975, and Schaeffer et al., 1984. These cancer potency factors were 0.82, 0.042, and 0.14, respectively (Table 4.3). The geometric mean cancer potency factor from these studies is 0.169 $(mg/kg/day)^{-1}$. If length of the experiment relative to the animal's lifespan is not corrected for in the analysis, the geometric mean of the cancer potency factor for 60% chlorine mixtures for these studies (Table 4.3) becomes 0.184 $(mg/kg/day)^{-1}$. Values used for this calculation were 0.98, 0.04 and 0.16, from the same respective studies. Thus, linear correction for length of lifespan makes very little difference in the derived cancer potency factor. Using this potency estimate and assuming a 1 per 100,000 acceptable risk for excess cancers, the derived daily dose is 0.0543 μg/kg/day.

5.0 A COMPARATIVE ANALYSIS OF THIS HAZARD EVALUATION IN LIGHT OF CURRENT REGULATORY POLICY

5.1 Comparative Analysis of Qualitative Issues

5.1.1 The USEPA Approach

When the toxicological literature regarding PCBs is examined, it is clear that there are substantial differences in toxicity among the individual PCB congeners. The levels of specific congeners can vary widely among commercial PCB mixtures of different chlorine content, accounting for the differences commonly observed among PCB mixtures in toxic effects and/or potency. While studies of nononcogenic, toxic effects of PCBs have readily demonstrated these differences, the traditional approach to evaluation of carcinogenic effects of PCBs has been to treat them as a single entity, i.e. data derived for one mixture are presumed to apply to all mixtures.

Rat bioassays examining 60% chlorine PCB mixtures have consistently found a substantial incidence of hepatic carcinoma with lifetime exposure. In one such study, serial biopsies detected evidence of a progression from the appearance of neoplastic nodules to carcinomas in the liver. Though it may be suspected that only one or a few PCB congeners in the 60% chlorine PCB mixtures may have been responsible for the tumorigenic effect, our present state of knowledge does not permit us to identify them.

The USEPA and others have argued that because the identities of the tumorigenic congeners in 60% chlorine content are unknown, it is prudent to assume that all PCB mixtures contain them and thereby possess carcinogenic potential (USEPA, 1988). As such, the less certain results from rodent bioassays of lesser chlorinated PCB mixtures are cast in a supporting role. That is, the neoplastic nodules seen with 42% chlorine PCB treatment in rats, and the neoplastic nodules and adenomas in 54% chlorine PCB-treated rats are considered to be part of a progression from hepatic lesion to the liver carcinomas observed in the 60% chlorine PCB studies. The carcinomas observed in mice with high-dose 54% chlorine PCB treatments are also suggested to support the 60%

chlorine PCB rat data and the conclusion that all PCBs are carcinogenic in animals.

As a consequence of assuming some PCB congener(s) present in 60% PCBs may be found to a lesser extent in all PCB mixtures, USEPA risk assessments for all PCB mixtures, regardless of composition, are driven by estimations of cancer risk. Thus, USEPA modeled data from one of the 60% chlorine PCB studies, using assumptions really developed for genotoxic carcinogens, and applied this estimate of the human cancer risk to all PCB mixtures.

5.1.2 Comparison With This Hazard Evaluation

This Hazard Evaluation differs fundamentally from the approach used by the USEPA in at least two ways: 1) The manner in which PCBs are considered, i.e., on a specific mixture-by-mixture basis rather than collectively; and 2) The interpretation of the results of animal testing of PCBs, particularly the data relevant to assessing the potential carcinogenicity of PCBs. The basis for these distinctions are outlined below.

5.1.2.1 Collective Versus Commercial Mixture-Specific Evaluation

Commercial PCB mixtures vary not only in average chlorine content, but also with respect to the concentrations of specific congeners. A wealth of data derived from animal studies of PCB congeners have revealed that their toxic potency can vary widely. The toxicity of individual PCB congeners appears to be a function of both the extent of chlorination and the positioning of chlorines on the biphenyl molecule. The importance of such differences in structure and chlorination have been recognized and incorporated in the USEPA's approach to evaluating the toxicity of polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), and various toxic potency factors have been assigned to specific PCDD and PCDF congeners or groups of isomers. However, in the case of PCBs, the obvious differences that congener groups might contribute to PCB mixtures has largely been ignored.

The Halogenated Organics Subcommittee of the USEPA's Scientific Advisory Board has examined the issue of differences in PCB congener toxicity and has stated that congener-specific toxicologic evaluation is a desirable goal for PCBs. However, at present, there is not a sufficient database on individual PCB congener effects to perform meaningful toxicological evaluations based on this approach. Recent research on PCBs indicates that there may be an additional problem in basing toxicological evaluations of PCBs on specific congeners. It appears from animal studies that some PCB congeners antagonize the toxicity of PCDDs (e.g., Haake et al., 1987; Bannister and Safe, 1987; Biegel et al., 1987), and are likely to inhibit the toxicity of other PCB congeners. The presence of significant PCB congener interactions would effectively preclude a toxicological evaluation based upon simple summation of congener-specific toxicities. Basing an evaluation on the concentrations and assumed potency of component PCB congeners, without considering congener interactions, may lead to substantial over-estimations of the toxicity from exposure to the PCB mixture. Ultimately, the only way to effectively determine the toxicity resulting from exposure to mixtures of PCB congeners is to test the toxicity of mixtures themselves.

Although it can be argued that PCB mixtures "weather" or change composition in the environment due to differential loss of congeners, the fact remains that commercial PCB mixtures represent reasonable approximations of the PCB congener mixtures to which humans are exposed. Since most of the toxicological data derived for PCBs are based on treatment with commercial mixtures, the data exist with which to conduct mixture-specific toxicological evaluations. Further, the apparent substantial differences in toxic potency among commercial mixtures indicate that such an approach is necessary in order to conduct meaningful toxicologic evaluations. Treating all PCBs as a single toxicologic entity, as the USEPA does, mischaracterizes the hazards associated with the lesser chlorinated PCB mixtures which form the majority of PCB mixtures dealt with today. We note that the Halogenated Organics Subcommittee of the USEPA's Scientific Advisory Board has reached similar conclusions regarding the use of mixture-specific data.

5.1.2.2 Interpretation of Animal Data Relevant to Assessing the Potential Carcinogenicity of PCBs

The second area of fundamental difference between this Hazard Evaluation and approaches taken in the past by the USEPA is in the interpretation and treatment of data related to potential carcinogenicity of PCBs. One such issue deals with the interpretation of rodent bioassay data for PCB mixtures other than those of 60% chlorine content. The basis for this difference extends from the fundamental difference described above, i.e. the consideration of PCB mixtures individually versus collectively.

As a consequence of the consideration of PCBs as a single toxicologic entity, the results from bioassays of different commercial PCB mixtures are viewed as essentially weaker or stronger versions of the same result. According to this reasoning, nodular hyperplasia and adenomas in studies of lesser chlorinated PCB mixtures are thought by USEPA to confirm the carcinogenic potential that has been demonstrated clearly for only 60% chlorine PCB mixtures. Since the only PCB mixtures for which there is unambiguous evidence for carcinogenicity are those of 60% chlorine content, the data for 60% chlorine PCB mixtures provide the principal basis for characterizing PCBs as carcinogens as well as the cancer potency estimate for all PCBs.

As discussed above, there are compelling reasons to evaluate the toxicity of commercial PCB mixtures individually. When this is done with respect to carcinogenic potential, the outcome of this process confirms its validity. That is, when PCB commercial mixtures are examined individually it becomes apparent that there are important differences in their carcinogenic potential in animals. Hepatic carcinomas have only been convincingly observed in mice with 54% chlorine PCBs, and neither mice nor rats develop hepatic carcinomas following long term treatment with high doses of 42% chlorine PCBs. One argument for considering PCBs collectively is that the same PCB congener, or congeners, responsible for the carcinogenic response to 60% chlorine PCBs in rats may also be present in other PCB mixtures. Even if this were true, the different results obtained from animal tests show that, for PCB mixtures such as those of 42% chlorine content, they do not elicit a carcinogenic response.

A related issue is the interpretation of the meaning of the hyperplastic nodules observed with 42% chlorine PCBs and to some extent with 54% chlorine PCBs. Because the hepatocellular carcinomas found in 60% chlorine PCB-treated rats appeared to develop in a progression from neoplasm or nodule to adenoma and finally carcinoma, the appearance of nodules in 42% and 54% PCB-treated rats is considered by some to be positive evidence for carcinogenicity. In the absence of lifetime exposure studies, the presence of these neoplastic lesions might be used to suggest the possibility of progression to carcinomas. However, these lesions are not cancer, and both 42% and 54% chlorine PCBs have in fact been tested for carcinogenicity in lifetime exposures in rats. While neoplastic lesions may appear in the rat liver after lifetime treatment with these PCB mixtures, the results from these studies tell us that they do not progress to carcinomas. Therefore, the use of the neoplastic lesions in 42% and 54% chlorine PCB-treated rats to assert that they are carcinogenic cannot be justified.

PCB mixtures of 42%, 54%, and 60% chlorine content have been individually examined for carcinogenic potential in rodent bioassays. This Hazard Evaluation has considered them individually, has taken the results at face value, and has employed no additional assumptions that cannot be scientifically justified. The data clearly indicate the potential for tumorigenesis in rats treated with 60% chlorine PCBs, although there are a number of qualitative issues to be considered in assessing the meaning of this result to human cancer. PCB mixtures of 42% chlorine PCB content did not produce elevated incidences of cancer in the liver or other tissues in either mice or rats. In the case of rats, exposure was at or near a maximally-tolerated dose for the lifetime of the animal. Just as the 60% chlorine PCB results indicate tumorigenic potential, the results with 42% chlorine PCBs indicate the absence of this potential. The results are more difficult to interpret with respect to 54% chlorine PCBs because the results in mice were positive while the results in rats were negative. The issue for 54% chlorine PCBs is simply which animal species is considered a more reliable model. Our opinion, and that of others, is that the rat is generally more reliable, and we have consequently chosen to evaluate 54% chlorine PCBs based upon noncarcinogenic toxicity rather than risk of carcinogenicity.

Although not crucial to this Hazard Evaluation, an additional difference in interpretation of the data relevant to potential carcinogenicity of PCBs is the issue of thresholds. The cancer potency estimate for all PCBs derived from 60% chlorine PCB data in rats assumes a linearized model, i.e. a nonthreshold approach. While the issue of thresholds is controversial in the regulatory arena, it is becoming widely accepted in the scientific community that a nonthreshold approach is only appropriate for carcinogens that are genotoxic. Those that are nongenotoxic, or work by epigenetic mechanisms, are thought by many to possess a threshold below which no carcinogenic effect will be observed. In fact, it can be argued that a nonthreshold assumption for nongenotoxic effects is difficult to defend on theoretical or empirical grounds.

Repeated studies have demonstrated that PCBs are not genotoxic. Therefore, any carcinogenic effect of PCBs would have to result from an epigenetic mechanism. A logical epigenetic mechanism for PCBs would be through the promotional stimulus provided by recurrent hepatotoxicity, and it should be noted that each of the rodent bioassays was conducted with severely hepatotoxic doses of PCBs. While the 60% chlorine PCB studies in rats were each conducted with only one dose, the multiple doses used in the 54% chlorine PCB studies in mice (the only other positive PCB carcinogenicity data) illustrate an association between dose and neoplastic changes that is clearly consistent with a mild promotional effect resulting from hepatic injury. The response to 54% chlorine PCBs in mice versus rats can be explained by the higher background tumor incidence in the mouse, and is also consistent with the known promotional effect of hepatotoxicity (Ward, 1989). The evidence therefore favors a mechanism for carcinogenicity of 60% chlorine PCBs in rats and 54% chlorine PCBs in mice that is threshold-dependent. Aside from the qualitative and quantitative problems of using 60% chlorine PCB carcinogenicity data to characterize other PCB mixtures, the linear, nonthreshold cancer potency estimation process employed by the USEPA for PCBs would appear to be scientifically inappropriate.

5.2 Comparative Analysis of the Quantitative Assessments

5.2.1 Comparative Analysis of the Quantitative Assessments For 60% PCB Mixtures

Currently, the USEPA applies a single cancer potency estimate to all PCB exposures. This cancer potency estimate is 7.7 per mg/kg/day^{-1}, and is based on the study by Norback and Weltman (1985). We have derived a similar value from these data when using their assumptions (see Table 4.4). However, we believe this number is a flawed estimate because of several problems associated with the experimental design of this study and because some of the assumptions used to generate this number are probably not valid. These problems are discussed in the following paragraphs.

The experimental design of the Norback and Weltman (1985) study violates NCI guidelines for chronic rodent bioassays. Partial hepatectomy was performed on a large portion of the animals used in this study, and partial hepatectomy is a well-known promotional stimulus for the liver cancer. Therefore, no reasonable reliance can be placed on the final cancer incidence measured in this study, because it may not all be attributable solely to PCB exposure.

Compounding this problem is the fact that the final tumor incidence was measured at 29 months rather than the typical 24 months. It is clear from this and other studies that the incidence of rat hepatocellular carcinomas increases with time and significant rates are observed only after extended intervals. Some may wish to argue that extending the duration of the bioassay enhances its sensitivity. However, our primary objection to this approach is that while it increases the tumor incidence of PCBs, it distorts the perceived PCB cancer potency relative to that measured for other chemical carcinogens. Further, because human mortality studies with PCBs indicate that this cancer potency estimation is exaggerated and overstates human risk, as will be shown in later paragraphs, use of this study instead of others with comparable findings does not seem justifiable.

A related problem with this study is the apparent exclusion of certain

animals which would also falsely inflate the final cancer incidence. As the cancer potency estimate is based on the incidence of tumors plus neoplastic nodules, and because these nodules were apparent by 12 months, the final statistical analyses should have been performed on animals that were alive 12 months or longer rather than the 18 months and longer interval reported by the authors. Since 70 animals started the experiment, the incidence for animals surviving 12 months or longer would be somewhere between 45/70 (64%) and the 45/47 (96%) actually used. Thus, the actual cancer potency estimate lies somewhere between 1.8 and 7.8 mg/kg/day^{-1}, ignoring all other problems with this study, depending upon the number of animals that died the first year.

Last, one point that would be of greater importance had the use of partial hepatectomy not invalidated reliance on the Norback and Weltman study is the fact that in one of the studies (Schaeffer et al., 1984), the authors attempted to use a PCB mixture of limited or no PCDF contamination so that a closer approximation of the cancer potency of PCBs would be measured. As Norback and Weltman made no similar effort, concern that the cancer potency derived from this study may be due in part to contamination of the test material is an additional confounder. Thus, there are a number of reasons why the USEPA's selection of the Norback and Weltman study over the Schaeffer et al. or Kimbrough et al. studies, or some mean value of all three bioassays as suggested by recent studies (Allen et al., 1987), cannot be justified; and this approach should not be condoned by using the new USEPA cancer potency estimate of 7.7 mg/kg/day^{-1} that is derived from a flawed study.

A number of questions about the USEPA approach can also be raised concerning the assumptions used in the mathematical modeling of the data. First, the choice of the scaling method used to extrapolate human doses from the rat doses is a controversial one. Three federal agencies (the Consumer Product Safety Commission, the Food and Drug Administration, and the Environmental Protection Agency) use three different methods to determine human doses from animal experiments. In particular, there is considerable debate as to whether body surface (mg of chemical/m^2 of body surface/day; favored by the EPA) or body weight (mg of chemical/kg body weight/day; favored by the FDA) scaling is more appropriate for determining human doses from animal data. As discussed in

section 4.0, the assumption that the human dose-response will be best mimicked by a surface area conversion of the dose increases the cancer potency estimate 6-7 fold.

The USEPA has adopted body surface dose conversions as a matter of policy, and we recognize that its application to PCBs is a result of this policy. However, recent evidence lends empirical support to scaling on the basis of body weight for animal carcinogens. In a rigorous analysis of risk assessment methods using data on 44 chemicals which allowed prediction of risk-related doses (RRD) from animal and human data, Allen et al. (1987) determined that if the appropriate analysis method were used, surface area conversion overestimates the RRD by a factor of 8 to 12 while a body weight conversion overestimates by a factor of only 1.1 to 1.7. These data support the use of body weight conversion for determining human equivalent dose; this change alone in the USEPA data set would reduce the cancer potency factor to 1.3 per mg/kg/day. We also find support for our position that body weight scaling is appropriate for PCBs in light of the fact that Crump and associates (Allen et al., 1987) used PCBs as one the test compounds validating the body weight scaling factor.

Again, the use of bioassays of extended duration in evaluating PCBs must be questioned. The fact that USEPA typically corrects for the length of the experiment when the duration is less than two years, but applies no correction when the duration is considerably greater than two years, seems to raise obvious inconsistencies in cancer potency derivations. The guidelines for NCI cancer bioassays are such that the typical exposure durations and animal lifetime are some 104 weeks (two years). The studies of Norback and Weltman (1985) and Schaeffer et al. (1984) are unique in that each study was conducted over a period of time greater than what is normally considered for a carcinogenicity bioassay. Their studies were conducted for periods of 119 and 125 weeks, respectively. According to the data of Schaeffer and coworkers, carcinomas did not appear prior to day 700 (100 weeks) and the majority (61%) of the carcinomas found at necropsy were found in animals sacrificed between days 801 and 832, i. e. weeks 114 to 119. Similarly, data from Norback and Weltman (1985) showed that trabecular carcinomas did not appear until the 15th month and that two of the three livers examined at the 18 and 24 month time periods had carcinoma;

adenocarcinoma was not found in the excised liver sections until the 24th month. Thus, if these experiments had been terminated at the point at which most carcinogenicity bioassays are stopped, the proportion of animals determined to have neoplastic lesions certainly would have been less; one is left to wonder how these data can be compared to studies with other chemicals whose results are measured at 104 weeks. Recognizing that cancer incidence and risk are a function of age in both animals and humans, using variable experimental time intervals among the different experimental chemical carcinogens regulated by the USEPA seems an obvious inconsistency in regulatory policy.

Another assumption that may be called into question is the combination of liver nodules with benign and malignant tumors. While the progression from various stages of neoplasia to tumor might be assumed to represent the normal evolution of liver tumors, there is no evidence that the nodules identified in any of the studies will progress to cancer. OSTP (1986) guidelines for cancer risk assessment do not suggest that rat liver is an organ where tumor progression and delineation is so broad that benign tumors should be combined with malignant tumors for analysis. More to the point, since cancer is the endpoint of interest and two of the tests were of longer than required duration, the inclusion of nodules which had not even progressed to benign tumors following a lifetime of exposure to PCBs is not an accurate portrayal of the cancer incidence. As the concept of latency or time-to-tumor suggests, latency will be increased with decreasing dose. Artificial magnification of the tumor incidence occurring at high doses causes an even greater exaggeration of the probable response expected at the much lower doses typically considered in risk assessments. Again, the assumption that nodules should be combined with malignant tumors ultimately causes the perceived cancer incidence (cancer potency estimate) to be falsely elevated. As shown in Table 4.3, this assumption enhances the mean potency estimate of all studies some four fold.

The last major problem associated with the cancer potency estimate that the USEPA has derived for 60% PCBs and applied to all PCB mixtures is that it does not appear to be a relevant measure of human potency. One problem common to many cancer potency estimates derived from animal data is that the multitude of conservative assumptions employed in the derivation of these estimates may yield

a number that is obviously inconsistent with fact. This can be easily demonstrated by estimating the human risk of occupational exposures based on the animal cancer potency estimate (James, 1985; Gehring, 1988). For example, applying the 7.7 $(mg/kg/day)^{-1}$ cancer potency factor derived by the EPA to the average occupational PCB dose of 50 μg/kg/day for an assumed occupational exposure duration of 10 years, an additional lifetime cancer risk of 5% (some 5 additional cancer deaths per 100 deceased) is calculated. Clearly, such a risk would be detectable in the epidemiological studies of worker populations conducted to date, particularly in the negative study of Nicholoson et al. (1987), since this entire population was consisted of persons with ≥ 5 years of work-related exposure. Similarly, some of the clinical studies involved populations with significant lengths of exposure, e.g., Fischbein et al. (1979) examined a population of which 40% (131/326) had ≥ 20 years exposure to PCBs. Thus, a clear inconsistency between the animal cancer potency estimate and current epidemiologic evidence is apparent; for according to the animal potency estimate a specific increase in cancer in a specific organ should have been easily demonstrable, yet no clear association has been found in human studies. Therefore, largely negative epidemiological data serve to indicate the implausibility of the PCB cancer risk estimates calculated according to EPA methods, particularly for those persons with long-term exposure.

In summary, we believe the current USEPA cancer potency estimate suffers from several methodological errors in study design and in assumptions incorporated into the mathematical modeling of the final estimate. The potency estimate derived in this Hazard Evaluation is thought to represent a reasonable compromise on the major issues, and it incorporates the suggestions made to the USEPA concerning cancer risk assessment methodologies (Allen et al., 1987). **Even if USEPA fails to consider and incorporate the improvements in risk assessment methodologies that have been identified recently, the obvious methodological shortcomings of the study it has selected raise serious questions about the reliability of the current approach. Therefore, we suggest USEPA reconsider its approach, and at the very least utilize the less problematic Schaeffer et al. (1984) study, or take some mean value derived from all of the data (as suggested by Allen et al., 1987), as a more representative cancer potency estimate.**

5.2.2 Comparative Analysis of the Quantitative Assessments For 54% PCB Mixtures

As previously stated, the current USEPA approach is to assume 54% PCB mixtures represent a quantitative hazard equivalent to 60% PCB mixtures. Because positive rat data do not exist for 54% mixtures, at the very minimum there are clear quantitative differences in the response that should be expected from these two mixtures. Thus, all of the problems identified for using the current USEPA cancer potency estimate for 60% chlorine mixtures are magnified when this number is applied to 54% PCB mixtures.

We have reviewed the evidence for the carcinogenicity of 54% chlorine PCB mixtures in humans and animals as well as studies examining the genotoxic potential of PCB mixtures. We have also reviewed the current scientific controversy concerning the relevance of mouse tumor data, as well as other features of the mouse data for 54% chlorine mixtures which tend to limit human relevance of the data. It is concluded that this information argues strongly against the use of nonthreshold quantitative modeling, and a threshold approach was therefore used to derive a safe exposure limit. The approach taken in this document is not inconsistent with USEPA policy. As discussed in section 3.0, the weight of evidence classification for 54% chlorine PCB mixtures indicate they should be classified as Group-C chemicals according to USEPA classification guidelines, and as Group-3 chemicals according to the IARC scheme. Group-C chemicals represent a gray area to the USEPA both in terms of classification and risk quantitation. Group-C is definitely a category for which the following USEPA guidance for cancer risk assessment is clearly intended:

> *When pharmacokinetic or metabolism data are available, or when other substantial evidence on the mechanistic aspects of the carcinogenesis process exists, a low-dose extrapolation model other than the linearized multistage procedure might be considered more appropriate on biological grounds. When a different model is chosen, the risk assessment should clearly discuss the nature and weight of evidence that led to the choice. Considerable uncertainty will remain concerning the response at low doses; therefore, in most cases an upper-limit risk estimate to using the linearized multistage procedure should also be presented.* (51 FR 33998)

Because of the sometimes equivocal or weak nature of the animal data for chemicals classified as Group-C carcinogens, this classification represents one in which the weight of the evidence determines whether a cancer risk is quantified or a threshold approach is applied to some other toxicologic endpoint to develop human exposure guidelines. And it is clear that when the USEPA believes the potential for human carcinogenicity is weak or insufficient, the Group-C chemical involved should not be regulated as a human carcinogen and threshold methods for quantitating the safe human dosage are used (e.g., USEPA's recent decision for linuron; 53FR31266; 1988). Therefore, the quantitative assessment for 54% PCBs in this document is consistent with USEPA policy given our qualitative assessment of the animal data.

We wish to point out that other endpoints and data might have been selected for the development of an ADI for 54% PCBs. But after careful consideration of these alternative approaches it is concluded that they offer little or no advantage to the approach we have selected, nor would their quantitative results be substantially different. The following paragraphs discuss these alternative approaches and their advantages or disadvantages.

One alternative approach would be to base the ADI on the estimated threshold for all animal toxicities as developed in section 3.0 of this report. The estimated NOAEL for 54% chlorine PCBs was 48 µg/kg/day. In developing an ADI from animal studies, the available human data cannot be ignored, particularly as they are relevant in determining the magnitude of safety factor that should be employed in extrapolating the animal results to humans. Since exposure estimates derived from the extensive occupational data available indicate an apparent NOAEL nearly identical to that seen in animals, a safety factor much less than 10 is warranted for interspecies extrapolation, perhaps 5. By incorporating the additional safety factor of 10 for sensitive individuals, the resulting ADI estimated from animal studies would be essentially identical to the 1 µg/kg/day value derived in the Hazard Evaluation from the occupational exposure data.

It is recognized that the carcinogenicity data for 54% chlorine PCBs are

contradictory, with mouse and rat bioassays giving opposing results. In our qualitative analysis, we have considered the rat to be a more reliable model and have consequently developed an ADI based on a toxicity other than cancer. If a different qualitative decision had been made, and a cancer endpoint used to establish the ADI, three approaches could have been used.

The first approach would be to base the extrapolation upon studies reporting a promotional effect of 54% chlorine PCBs on the liver carcinogenicity of other agents, such as diethylnitrosamine in rats. This promotional mechanism is also considered to have an inherent threshold, and Deml and Oesterle (1987) have determined the threshold for this effect in weanling rats to be a dose of 0.43 mg/kg/day. Using this NOAEL, and applying the 100-fold safety factor, a value typically used when extrapolating from animal data, a final ADI of 4.3 µg/kg/day is calculated.

Since positive bioassay data for 54% chlorine PCB mixtures are confined to the mouse, and because these data and other lines of evidence clearly indicate a threshold-dependent mechanism, an estimation of the threshold dose for tumorigenicity in the mouse could be made. Doses of 500 ppm 54% chlorine PCBs produced malignancies in mice over the 32-week period of the study by Ito and coworkers (Ito et al., 1973a&b), while doses of 250 and 100 ppm produced no neoplastic lesions. The 250 ppm dose corresponds to about 37.5 mg/kg/day. Applying a safety factor of 100 yields an ADI of 375 µg/kg/day. It should be noted that if a safety factor of 1,000 or even 10,000 had been selected for this approach (although the considerable human evidence would seem to preclude using a safety factor this large), the final ADI generated would be 37.5 µg/kg/day and 3.75 µg/kg/day, respectively. These values are still higher than our proposed conservative ADI, and so offer no advantage over the approach we have used in this report.

The third approach would be to calculate a potency factor from the mouse data. Regardless of the fact that there are significant methodological problems with the animal bioassay data for 54% chlorine PCB mixtures, the positive data can still be subjected to the linearized multistage analysis. Nagasaki et al. (1974) reported hepatocellular carcinoma in male mice exposed to dietary levels of

Kanechlor 500 of 500 ppm for a 32-week period. Exposure to dietary levels of 0, 100 or 250 ppm for the same time period did not result in the development of carcinomas. Using these data, a cancer potency factor of 0.0019 $(mg/kg/day)^{-1}$ can be derived using the same assumptions as described for the factors derived for 60% chlorine PCB mixtures. If this potency factor is applied to our recommended ADI for 54% chlorine PCB mixtures, the ADI of 1 µg/kg/day we have selected would represent an assumed lifetime risk of 1.9×10^{-6}. Thus, even assuming that the weak animal data for the carcinogenicity of 54% chlorine PCB mixtures may be reliable, our ADI of 1 µg/kg/day provides sufficient protection to be used as a chronic human exposure guideline. While we note that even the USEPA does not consider the mouse data robust enough for the derivation of a cancer potency factor, and we agree that this should not be done, to do so would only confirm that our recommended ADI implies a risk within what is a currently accepted guideline (i.e., 1×10^{-4} to 1×10^{-6}).

The qualitative decision to develop an ADI for 54% chlorine PCBs based on nononcogenic toxicity is in our opinion the most valid. However, from the preceding analysis it is apparent that even if the opposite decision had been reached, i.e. to use the carcinogenicity bioassay and tumor promotion studies of 54% chlorine PCBs to generate an ADI, the result would be at least as conservative or only slightly different.

Based on the preceding analysis, the final value we have selected for a cancer potency factor represents a reasonable compromise for a chemical with limited animal cancer data of questionable human relevance. Taking a threshold approach to the human data recognizes the epigenetic, threshold-dependent mechanism for the carcinogenic effects of PCBs in animals. On the other hand, the final number is low enough that it is equivalent to a conservative, nonthreshold, linear extrapolation of the animal data to a dose approximating a 10^{-6} risk. [Note: A 10^{-5} risk is considered acceptable here because it would be less than the drinking water risk posed by several USEPA drinking water standards (see Table 5.1). A 10^{-5} risk is also acceptable under the Massachusetts Contingency Plan, 310 CMR 40.545.] Therefore, we propose that a 1 µg/kg/day ADI is consistent with the intent of both USEPA and Massachusetts public health policy.

Table 5.1

Lifetime Risks Posed by USEPA Drinking Water Standards†

Carcinogen (mg/l)	Classification* Lifetime Risk (x 10-5)		MCL
Drinking water standard:			
Arsenic**	A	50	250
Carbon tetrachloride	B2	5	1.86
Chloroform	B2	100	23.1
Toxaphene	B2	5	15.7
Vinyl chloride	A	2	13.1
TSCA soil clean-up guideline for PCBs:			
Resident	B2	10 ppm	0.17
Worker	B2	50 ppm	0.12

† Adapted from USEPA (1986a)

* Under the USEPA classification scheme a class A chemical carcinogen is known to be carcinogenic in humans, a class B2 is a considered to be a probable human carcinogen even though there is only sufficient evidence in animals.

** Based on the revised cancer potency factor of 5 x 10-5 (µg/l)-1 published in Inside EPA Weekly Report, Vol. 8, No. 52, December 25, 1987, as recommended by the EPA Risk Assessment Council.

In summary, we conclude that the 1 µg/kg/day ADI calculated in this document from the human exposure data represents a reasonable quantitative compromise for this Group-C class of compounds because it represents a conservative estimate striking a reasonable numerical balance between concern for the limited carcinogenic potential of this mixture and other toxic effects of equal concern. The final number is equivalent to applying the following safety factors to the following endpoints, each of which has a demonstrable threshold: 1) a safety factor of 50 to the estimated NOAEL for all animal toxicities, keeping in mind that there is considerable evidence that humans have experienced

considerably higher exposures without adverse effect; 2) a safety factor of 430 to the threshold dose for liver tumor promotion in weanling rats; and 3) a safety factor of ≥ 37,500 to the NOAEL for liver cancer in mice. Finally, this number is considered reasonably conservative because it approximates the 10^{-6} risk level for liver cancer should the questionable approach of modeling the limited mouse data be attempted.

5.2.3 Comparative Analysis of the Quantitative Assessments for 42% PCB Mixtures

The USEPA approach to quantitative assessment for 42% chlorine PCB mixtures, as described in previous sections, is to assume carcinogenic potential equivalent to 60% chlorine PCB mixtures and apply a cancer potency estimate based on 60% chlorine PCB bioassay data. However, as indicated in previous sections, the data clearly demonstrate that 42% chlorine PCB mixtures are not equivalent to 60% chlorine PCBs in carcinogenic potential. In section 3 of this Hazard Evaluation we have concluded that 42% chlorine PCB mixtures should be classified as Group-D chemicals according to the USEPA classification scheme and as Group-3/Group-4 chemicals according to the IARC classification guidelines. This indicates that a carcinogenic potential cannot be deduced from the data set currently available. In fact, since no positive data exist, it is not possible to model the data set to derive a cancer potency estimate.

The approach taken instead has been to derive an ADI based upon clinical studies of individuals exposed occupationally to PCBs including those of 42% chlorine content. The ADI derived from this analysis, including a safety factor to protect sensitive individuals, was 5 μg/kg/day. Alternatively, an ADI could have been estimated based on animal data with 42% chlorine PCBs. The estimated animal NOAEL was 100 μg/kg/day. Since there are both extensive animal and human data available, it is unlikely that a full safety factor of 10 would be required for interspecies extrapolation, especially since the human data indicate an apparent NOAEL within a factor of 2. Consequently, even if an additional safety factor of 10 is applied (e.g. for sensitive individuals), the ADI derived from animal data would not be significantly different from that generated from human data. Therefore, while it is our opinion that the strongest basis for establishing an ADI

for 42% chlorine PCBs is through the human data, in practice an ADI developed from animal data yields the same answer.

6.0 REFERENCES

6.0 REFERENCES

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